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L6 ANSWER 1 OF 1 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 134:290390 CA
TITLE: Dihydroorotate dehydrogenase inhibitors, and use with other agents, for the treatment of virus-mediated diseases
INVENTOR(S): Tan, Yin Hwee; Driscoll, John Stanford; Mui Mui, Sim
PATENT ASSIGNEE(S): Institute of Molecular and Cell Biology, Singapore; Mui Mui, Sim
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

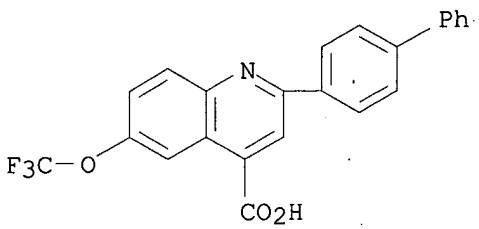
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001024785	A2	20010412	WO 2000-US26797	20000929
WO 2001024785	A3	20020711		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1237546	A2	20020911	EP 2000-965517	20000929
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003510352	T2	20030318	JP 2001-527784	20000929

PRIORITY APPLN. INFO.: US 1999-157017P P 19991001
WO 2000-US26797 W 20000929

OTHER SOURCE(S): MARPAT 134:290390

AB Flavivirus, rhabdovirus, and paramyxovirus infections may be treated by administering an inhibitor of dihydroorotate dehydrogenase, e.g. 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinolinearcarboxylic acid sodium salt (Brequinar). A synergistic effect can be obtained if an interferon, e.g. interferon .alpha.2, interferon .alpha.8 or interferon .beta., or an inhibitor of a second enzyme selected from inosine monophosphate dehydrogenase, guanosine monophosphate synthetase, cytidine triphosphate synthetase and S-adenosylhomocysteine hydrolase, is also administered. Compd. prepn. is described.

IT **333969-73-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dihydroorotate dehydrogenase inhibitors, and use with other agents, for the treatment of virus-mediated diseases)
RN 333969-73-6 CA
CN 4-Quinolinecarboxylic acid, 2-[1,1'-biphenyl]-4-yl-6-(trifluoromethoxy)- (9CI) (CA INDEX NAME)



IT **333969-73-6P 333969-74-7P 333969-75-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dihydroorotate dehydrogenase inhibitors, and use with other agents, for the treatment of virus-mediated diseases)

IT **96187-27-8 96187-30-3 96187-53-0 96201-22-8 96201-88-6 130507-59-4 333969-81-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydroorotate dehydrogenase inhibitors, and use with other agents, for the treatment of virus-mediated diseases)

=> d ibib abs fhitstr hitrn 1-13

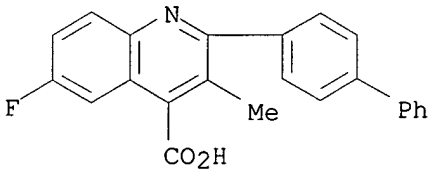
L9 ANSWER 1 OF 13 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 138:283178 CA
TITLE: Methodology and problems of protein-ligand docking: case study of dihydroorotate dehydrogenase, thymidine kinase, and phosphodiesterase 4
AUTHOR(S): Pospisil, Pavel; Kuoni, Thomas; Scapozza, Leonardo; Folkers, Gerd
CORPORATE SOURCE: Department of Applied Biosciences, Swiss Federal Institute of Technology (ETH) Zurich, Zurich, CH-8057, Switz.
SOURCE: Journal of Receptors and Signal Transduction (2002), 22(1-4), 141-154
CODEN: JRSTCT
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The docking methodol. was applied to three different therapeutically interesting enzymes: human dihydroorotate dehydrogenase (DHODH), Herpes simplex **virus** type I thymidine kinase (HSV1 TK) and human phosphodiesterase 4 (PDE4). Programs FlexX, AutoDock and DOCK where used. The three targets represent three distinct cases. For DHODH and HSV1 TK, the binding modes of substrate and inhibitors within the active site are known, while the binding orientation of cAMP within PDE4 has been solely hypothesized. Active site of DHODH is mainly hydrophobic and the binding mode of the inhibitor brequinar was used as a template for evaluating the docking strategies. The presence of cofactors revealed to be crucial for the definition of the docking site. The HSV1 TK active site is small and polar and contains crystal water mols. and ATP. Docking of thymidine and aciclovir (ACV) within the active site was analyzed by keeping or removing water mols. It showed the crucial role of water in predicting the binding of pyrimidines and purines. The crystal structure of PDE4 contains magnesium and zinc cations as well as catalytic water mol. but no ligand.

Several docking expts. of cAMP and rolipram were performed, and the results showed clear-cut dependence between the ligand orientation and the presence of metals in the active site. All three cases show specific problems of the docking methodol., depending on the character of the active site.

IT **96187-27-8**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(methodol. and problems of protein-ligand docking in the cases of dihydroorotate dehydrogenase, thymidine kinase, and phosphodiesterase 4)

RN 96187-27-8 CA
CN 4-Quinolinecarboxylic acid, 2-[1,1'-biphenyl]-4-yl-6-fluoro-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-27-8 96187-53-0**, Brequinar
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(methodol. and problems of protein-ligand docking in the cases of dihydroorotate dehydrogenase, thymidine kinase, and phosphodiesterase 4)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

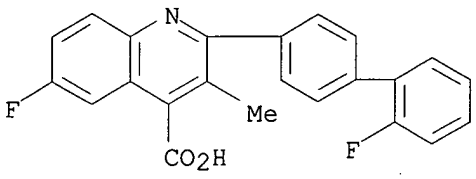
L9 ANSWER 2 OF 13 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 138:83366 CA
TITLE: Combination therapy for the treatment of immunological disorders
INVENTOR(S): Lindner, Juergen
PATENT ASSIGNEE(S): Aventis Behring G.m.b.H., Germany
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1275638	A1	20030115	EP 2002-13275	20020618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
DE 10132308	A1	20030130	DE 2001-10132308	20010706
US 2003017166	A1	20030123	US 2002-189006	20020705
JP 2003063995	A2	20030305	JP 2002-196842	20020705

PRIORITY APPLN. INFO.: DE 2001-10132308 A 20010706
OTHER SOURCE(S): MARPAT 138:83366

AB The invention provides a combination treatment for excessive injurious immune reactions and degenerative processes, which contains (a) at least one undesired immune reaction- or degenerative process-participating antigen; (b) at least one protein synthesis inhibitor; and, if necessary, (c) an agent for suppressing an acute inflammatory reaction.

IT **96187-53-0**, Brequinar
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy for treatment of immunol. disorders)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy for treatment of immunol. disorders)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 13 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 137:346188 CA
TITLE: Mini-adenoviral vector and methods of using same
INVENTOR(S): Fang, Xiangming; Hariharan, Mangala J.
PATENT ASSIGNEE(S): Genstar Therapeutics Corp., USA
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088319	A2	20021107	WO 2002-US13661	20020501
WO 2002088319	A3	20030306		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-287850P P 20010501

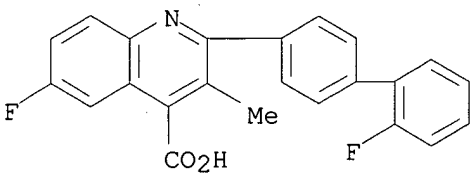
AB The present invention provides a method for treating a disorder such as hemophilia. A method of treating in a mammal by administering recombinant **virus** virions comprising a nucleotide sequence having an adenoviral inverted terminal repeat fusion sequence, packaging signal, a transcriptional control region, and a nucleic acid encoding a therapeutic protein such as FVIII. In addn., the DNA mol. does not encode an adenoviral protein. It is preferred that the virions be administered to the mammal under conditions that result in the expression of the therapeutic protein at a level that provides a therapeutic effect in said mammal. In addn., the virions are administered with immunosuppressive

agents.

IT **96201-88-6**, Brequinar sodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mini-adenoviral vector and methods of using same)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mini-adenoviral vector and methods of using same)

L9 ANSWER 4 OF 13 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 137:88442 CA

TITLE: Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms

INVENTOR(S): Shanahan-Pendergast, Elisabeth

PATENT ASSIGNEE(S): Ire.

SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-IE1	20020102
WO 2002053138	A3	20020919		

W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG

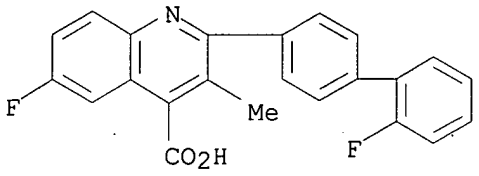
PRIORITY APPLN. INFO.: IE 2001-2 A 20010102

OTHER SOURCE(S): MARPAT 137:88442

AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immundysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixt. showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

IT **96201-88-6**, Brequinar Sodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(pharmaceutical formulation further including; incensole and furanogermacrens and compds. as antitumor and antimicrobial agents)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar Sodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation further including; incensole and furanogermacrens and compds. as antitumor and antimicrobial agents)

L9 ANSWER 5 OF 13 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 133:187987 CA
TITLE: Methods using pyrimidine-based nucleosides for treatment of mitochondrial disorders
INVENTOR(S): Naviaux, Robert K.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050043	A1	20000831	WO 2000-US4663	20000223
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
NZ 513926	A	20010928	NZ 2000-513926	20000223
BR 2000008447	A	20020115	BR 2000-8447	20000223
EP 1171137	A1	20020116	EP 2000-910321	20000223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537340	T2	20021105	JP 2000-600654	20000223

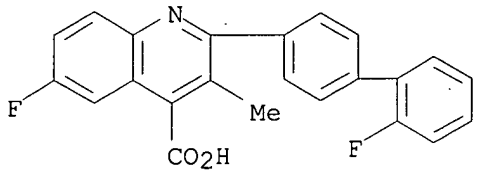
PRIORITY APPLN. INFO.: US 1999-121588P P 19990223
WO 2000-US4663 W 20000223
OTHER SOURCE(S): MARPAT 133:187987
AB Methods are provided for the treatment of mitochondrial disorders. The

methods include the administration of a pyrimidine-based nucleoside, e.g. triacetyluridine. Also provided are methods of reducing or eliminating symptoms assocd. with mitochondrial disorders. Mitochondrial disorders particularly appropriate for treatment include those attributable to a deficiency of one or more pyrimidines.

IT **96187-53-0**, Brequinar
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(pyrimidine-based nucleoside for treatment of mitochondrial disorder)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(pyrimidine-based nucleoside for treatment of mitochondrial disorder)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 13 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 132:334285 CA

TITLE: Preparation of phenyloxoazapropylcycloalkane derivatives and analogs as potassium channel inhibitors

INVENTOR(S): Baker, Robert K.; Chee, Jennifer; Bao, Jianming; Garcia, Maria L.; Kaczorowski, Gregory J.; Kotliar, Andrew; Kayser, Frank; Liu, Chou Juitsai; Miao, Shouwu; Rupprecht, Kathleen M.; Parsons, William H.; Schmalhofer, William A.; Claiborne, Christopher F.; Liverton, Nigel; Claremon, David A.; Thompson, Wayne J.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 243 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

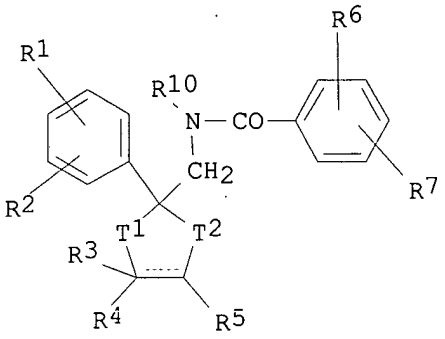
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000025770	A1	20000511	WO 1999-US24949	19991026
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1143965	A1	20011017	EP 1999-955159	19991026
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO
JP 2002528490 T2 20020903 JP 2000-579211 19991026
PRIORITY APPLN. INFO.: US 1998-106416P P 19981030
WO 1999-US24949 W 19991026
OTHER SOURCE(S): MARPAT 132:334285
GI



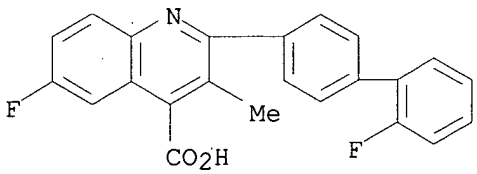
I

AB The title compds. I [T1 = (CH2)x; T2 = (CH2)y; dotted line indicates a single bond or double bond; x, y = 0 - 2; R1, R2, R6, R7 = halo, hydroxy, alkyl, etc.; R3, R4 = H, cyano, nitro, etc.; further details on R3 and R4 are given; R5 = H, halo, hydroxy, etc.; further details on R3 and R5 are given; R10 = H, etc.], useful as potassium channel inhibitors (no data), are prepd. I are useful in the treatment of autoimmune disorders, cardiac arrhythmias (no data), etc. Formulations are given.

IT **96201-88-6**, Brequinar sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of phenyloxoazapropylcycloalkane derivs. and a second drug)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



IT **96201-88-6**, Brequinar sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of phenyloxoazapropylcycloalkane derivs. and a second drug)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

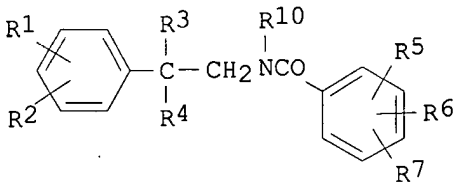
L9 ANSWER 7 OF 13 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 132:308139 CA
TITLE: Preparation of benzamide potassium channel inhibitors
INVENTOR(S): Baker, Robert K.; Kayser, Frank; Bao, Jianming; Kotliar, Andrew; Parsons, William H.; Rupprecht, Kathleen M.; Claiborne, Christopher F.; Liverton, Nigel; Claremon, David A.; Thompson, Wayne J.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000025774	A1	20000511	WO 1999-US25042	19991026
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6194458	B1	20010227	US 1999-422499	19991021
EP 1126836	A1	20010829	EP 1999-971316	19991026
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002528493	T2	20020903	JP 2000-579215	19991026

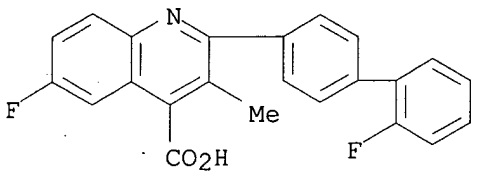
PRIORITY APPLN. INFO.: US 1998-106422P P 19981030
WO 1999-US25042 W 19991026

OTHER SOURCE(S): MARPAT 132:308139
GI



I

AB The title compds. I [R1, R2, R3, R4, R5, R6, R7 independently = halo, H, OH, (C1-6)-alkyl, Ph, PhO, CN, NO2, CO2H, N3, etc; R10 = H, (CO2)-aryl, (CO2)(C1-6)-alkyl, a proviso is given], useful as potassium channel inhibitors (no data), are prepd. Formulations are given.
IT **96201-88-6**, Brequinar sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of benzamide and another pharmaceutical)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of benzamide and another pharmaceutical)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 13 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 130:119591 CA
TITLE: Antioxidant enhancement of therapy for hyperproliferative conditions
INVENTOR(S): Chinery, Rebecca; Beauchamp, R. Daniel; Coffey, Robert J.; Medford, Russell M.; Wadsinski, Brian
PATENT ASSIGNEE(S): Atherogenics, Inc., USA
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9901118	A2	19990114	WO 1998-US13750	19980701
WO 9901118	A3	19990422		
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9882827	A1	19990125	AU 1998-82827	19980701
EP 1019034	A2	20000719	EP 1998-933078	19980701
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002511878	T2	20020416	JP 1999-507360	19980701
US 2001049349	A1	20011206	US 2001-779086	20010207

PRIORITY APPLN. INFO.:
US 1997-886653 A 19970701
US 1997-967492 A 19971111
US 1998-108609 B1 19980701
WO 1998-US13750 W 19980701

OTHER SOURCE(S): MARPAT 130:119591

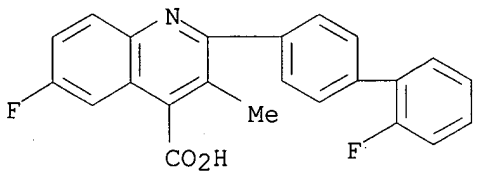
AB A method to enhance the cytotoxic activity of an antineoplastic drug comprises administering an effective amt. of the antineoplastic drug to a host exhibiting abnormal cell proliferation in combination with an effective cytotoxicity-increasing amt. of an antioxidant. The invention also includes a method to decrease the toxicity to an antineoplastic agent or increase the therapeutic index of an antineoplastic agent administered

for the treatment of a solid growth of abnormally proliferating cells, comprising administering an antioxidant prior to, with, or following the antineoplastic treatment.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antioxidant enhancement of therapy for hyperproliferative conditions)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antioxidant enhancement of therapy for hyperproliferative conditions)

L9 ANSWER 9 OF 13 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 129:241631 CA

TITLE: Expression, purification, and characterization of histidine-tagged rat and human flavoenzyme dihydroorotate dehydrogenase

AUTHOR(S): Bader, Benjamin; Knecht, Wolfgang; Fries, Markus; Loffler, Monika

CORPORATE SOURCE: Institute for Physiological Chemistry, School of Medicine, Philipps-University, Marburg, D-35033, Germany

SOURCE: Protein Expression and Purification (1998), 13(3), 414-422
CODEN: PEXPEJ; ISSN: 1046-5928

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

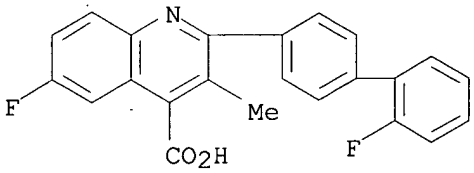
AB Mitochondrially bound dihydroorotate-ubiquinone oxidoreductase (dihydroorotate dehydrogenase, E.C. 1.3.99.11) catalyzes the fourth sequential step in the de novo synthesis of uridine monophosphate. Based on the recent functional expression of the complete rat dihydroorotate dehydrogenase by means of the baculovirus expression vector system in Trichoplusia ni cells, a procedure is described that allows the purifn. of baculovirus expressed enzyme protein fused to a carboxy-terminal tag of eight histidines. Exts. from mitochondria of Spodoptera frugiperda cells **infected** with the recombinant **virus** using Triton X-100 were loaded onto Ni2+-nitrilotriacetic acid agarose and histidine-tagged rat protein was selectively eluted with imidazole-contg. buffer. In view of our previously published work, the quality of the electrophoretic homogenous rat enzyme was markedly improved; specific activity was 130-150 .mu.mol dihydroorotate/min per mg; and the stoichiometry of flavin

content was 0.8-1.1 mol/mol protein. Efforts to generate mammalian dihydroorotate dehydrogenases with low prodn. costs from bacteria resulted in successful overexpression of the carboxy-terminal-modified rat and human dihydroorotate dehydrogenase in XL-1 Blue cells. By employing the metal chelate affinity chromatog. under native conditions, the histidine-tagged human enzyme was purified with a specific activity of 150 .mu.mol/min/mg and the rat enzyme with 83 .mu.mol/min/mg, resp., at pH 8.0-8.1 optimum. Kinetic consts. of the recombinant histidine-tagged rat enzyme from bacteria (dihydroorotate, Km = 14.6 .mu.M; electron acceptor decylubiquinone, Km = 9.5 .mu.M) were close to those reported for the enzyme from insect cells, with or without the affinity tag. HPLC analyses identified FMN as cofactor of the rat enzyme; UV-vis and fluorometric analyses verified a flavin/protein ratio of 0.8-1.1 mol/mol. By spectral analyses of the functional flavin with the native human enzyme, the interaction of the pharmacol. inhibitors Leflunomide and Brequinar with their target could be clarified as interference with the transfer of electrons from the flavin to the quinone. The combination of the bacterial expression system and metal chelate affinity chromatog. offers an improved means to purify large quantities of mammalian membrane-bound dihydroorotate dehydrogenases which, by several criteria, possesses the same functional activities as non-histidine-tagged recombinant enzymes. (c) 1998 Academic Press.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(expression, purifn., and characterization of histidine-tagged rat and human flavoenzyme dihydroorotate dehydrogenase)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(expression, purifn., and characterization of histidine-tagged rat and human flavoenzyme dihydroorotate dehydrogenase)

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 13 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 127:13451 CA

TITLE: Triterpene derivatives with immunosuppressant activity, their preparation, and compositions containing them

INVENTOR(S): Baker, Robert K.; Bao, Jianming; Kayser, Frank; Parsons, William H.; Rupprecht, Kathleen M.

PATENT ASSIGNEE(S): Merck and Co., Inc., USA; Baker, Robert K.; Bao, Jianming; Kayser, Frank; Parsons, William H.; Rupprecht, Kathleen M.

SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

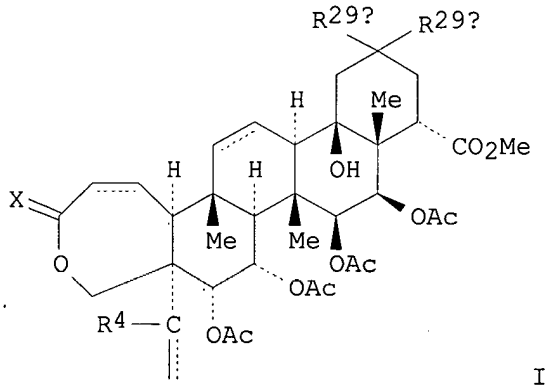
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9716068	A1	19970509	WO 1996-US17211	19961028
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9674781	A1	19970522	AU 1996-74781	19961028
AU 712015	B2	19991028		
EP 877554	A1	19981118	EP 1996-937010	19961028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 11514648	T2	19991214	JP 1996-517439	19961028

PRIORITY APPLN. INFO.:

US 1995-8169	19951031
US 1995-8189	19951031
GB 1996-3833	19960223
GB 1996-5156	19960312
WO 1996-US17211	19961028

OTHER SOURCE(S): MARPAT 127:13451
GI

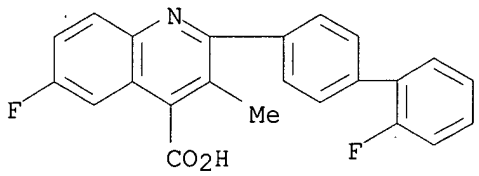


I

AB Compds. I [X= O, S, NH, or H and R1; a = single bond, double bond when R4 absent; b,c = single bond, double bond; R1, R2 = H, (un)substituted C1-6 alkyl; R4 = absent (a = double bond), H, OH, :O, etc.; R29a, R29b = H, :O, (CH2)sOH, (CH2)sNR1R2, etc.; s = 0, 1] are useful as immunosuppressive agents. Compds. of the invention produce a blockade of the KV1.3 voltage-gated potassium channel. Isolation of compds. from Spachea correa, synthetic prepn. of compds., and pharmaceutical compns. are described.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpene derivs. with immunosuppressant activity, prepn., and

(combination) compns.)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)

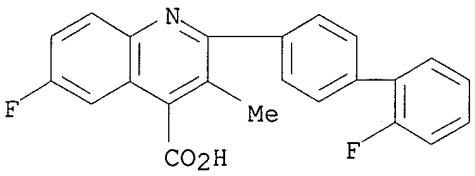


● Na

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpene derivs. with immunosuppressant activity, prepn., and (combination) compns.)

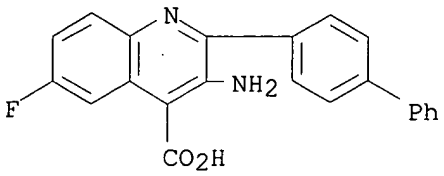
L9 ANSWER 11 OF 13 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 124:164405 CA
TITLE: Antiviral activity of inhibitors of pyrimidine de-novo biosynthesis
AUTHOR(S): Wachsman, M.; Hamzeh, F. M.; Assadi, N. B.; Lietman, P. S.
CORPORATE SOURCE: Department Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, 21287, USA
SOURCE: Antiviral Chemistry & Chemotherapy (1996), 7(1), 7-13
CODEN: ACCHEH; ISSN: 0956-3202
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Evaluation of the elevation of host cell biosynthesis of deoxynucleoside triphosphates (dNTP's) induced by human cytomegalovirus (HCMV) **infection** as a target for antiviral therapeutics was carried out. The concns. of all four intracellular dNTP's rose rapidly following HCMV **infection**, and were markedly above baseline by 8 h post **infection** (p.i.). All four deoxynucleoside triphosphates remained elevated above baseline for at least 72 h p.i. The effects of inhibitors of the de-novo pathway of pyrimidine biosynthesis on HCMV viral replication were quantified by DNA dot blot. All pyrimidine biosynthesis inhibitors examd. inhibited the HCMV DNA replication at concns. that were non-toxic to the cell. These drugs were also more effective against HCMV, which is highly dependent on host de-novo synthesis, than against HSV-1 which encodes enzymes capable of increasing the supply of dNTP's. The antiviral effect of brequinar, an inhibitor of one of the enzymes of the d-novo pathway (dihydroorotate dehydrogenase), was examd. to det. if it coincided with a decrease in dNTP's. HCMV-**infected** fibroblasts and uninfected control cells were treated with a concn. of brequinar able to inhibit HCMV DNA levels 90%. It was found that brequinar markedly lowered the levels of dTTP found in treated cells compared to untreated cells in both HCMV-**infected** and uninfected cells.
IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(antiviral activity of inhibitors of pyrimidine de-novo biosynthesis against human cytomegalovirus in human cells)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral activity of inhibitors of pyrimidine de-novo biosynthesis against human cytomegalovirus in human cells)

L9 ANSWER 12 OF 13 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 118:160590 CA
TITLE: Studies on the effect of CL 306,293, a substituted quinoline carboxylic acid, on the clinical disease induced in mice with LP-BM5 **virus**
AUTHOR(S): Scott, Jeffery W.; DeJoy, Susan Quinn; Jeyaseelan, Robert; Powell, Dennis W.; Raventos-Suarez, Carmen; O'Hara, Bryan; Wick, Michael M.; Oronsky, Arnold L.; Kerwar, S. S.
CORPORATE SOURCE: Med. Res. Div., American Cyanamid Co., Pearl River, NY, 10965, USA
SOURCE: Antiviral Research (1993), 20(1), 71-81
CODEN: ARSRDR; ISSN: 0166-3542
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CL 306,293, a substituted quinoline carboxylic acid, is a potent inhibitor of dihydroorotic acid dehydrogenase, an enzyme essential for the biosynthesis of pyrimidines. In mammalian cell culture, the agent exhibits antiproliferative properties that can be reversed by the addn. of uridine. CL 306,293 inhibits the development of the clin. disease in a murine model of immunodeficiency induced by a mixt. of LP-BM5 retroviruses. In **infected** mice, the agent prevents the development of hypergammaglobulinemia, lymphadenopathy, splenomegaly and induction of an IL-2 deficiency. The CD4/CD8 ratio and the no. of B cells in the lymph nodes are decreased if the **infected** animals are treated with CL 306,293. CL 306,293 was more efficacious and potent than 3'-azido-3'-deoxythymidine. The beneficial effects of CL 306,293 obsd. in this model are most probably related to its antiproliferative properties.
IT **131745-25-0**, CL 306293
RL: BIOL (Biological study)
(MAIDS from LP-BM5 retrovirus treatment with)
RN 131745-25-0 CA
CN 4-Quinolinecarboxylic acid, 3-amino-2-[1,1'-biphenyl]-4-yl-6-fluoro- (9CI) (CA INDEX NAME)



IT **131745-25-0**, CL 306293
RL: BIOL (Biological study)
(MAIDS from LP-BM5 retrovirus treatment with)

L9 ANSWER 13 OF 13 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 106:119710 CA
TITLE: Preparation and formulation of substituted quinolines as antibacterial and antitumor agents
INVENTOR(S): Atwell, Graham John; Denny, William Alexander; Rewcastle, Gordon William
PATENT ASSIGNEE(S): Development Finance Corp. of New Zealand, N. Z.
SOURCE: Eur. Pat. Appl., 44 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 206802	A2	19861230	EP 1986-304820	19860623
EP 206802	A3	19880713		
EP 206802	B1	19930901		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 62048669	A2	19870303	JP 1986-146771	19860623
JP 07064819	B4	19950712		
AT 93853	E	19930915	AT 1986-304820	19860623
US 4904659	A	19900227	US 1988-266243	19881028

PRIORITY APPLN. INFO.:
NZ 1985-212525 19850624
EP 1986-304820 19860623
US 1986-877556 19860623

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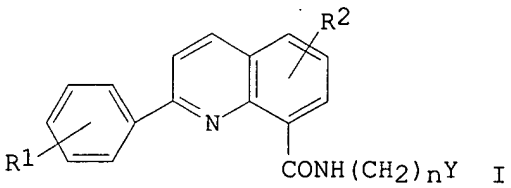


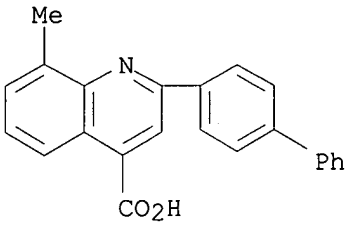
AB The title compds. [I; R1, R2 = H, alkyl, halo, F3C, cyano, MeSO2, NO2, OH, NH2, (un)substituted Ph; Y = C(:NH)NH2, HNC(:NH)NH2, NR3R4; R3, R4 = (un)substituted alkyl; NR3R4 = heterocyclyl; n = 2-6; in each of the carbocyclic rings 1 or 2 CH may be replaced by N] and their salts and 1-oxides, useful as bactericides (no data) and antitumor agents, were prepd. 2-MeC6H4NH2 was cyclocondensed with MeCOCO2H and BzH and the resulting quinolinecarboxylic acid was decarboxylated and oxidized to give

2-phenyl-8-quinolinecarboxylic acid; the latter was treated with 1,1'-carbonyldiimidazole and H2NCH2CH2NMe2 to give I (R1 = R2 = H, Y = NMe2, n = 2) (II). II had an IC50 of 1300 nM against L1210 leukemia cell cultures over 70 h and at 100 mg/kg i.p. showed an increase in lifespan of 91% in mice **infected** with P388 leukemia.

IT **107027-46-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and decarboxylation of)

RN 107027-46-3 CA

CN 4-Quinolinecarboxylic acid, 2-[1,1'-biphenyl]-4-yl-8-methyl- (9CI) (CA INDEX NAME)



IT **107027-46-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and decarboxylation of)

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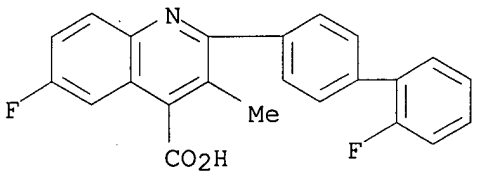
L14 ANSWER 1 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 138:267574 CA
TITLE: Plant **dihydroorotate** dehydrogenase differs significantly in substrate specificity and inhibition from the animal enzymes
AUTHOR(S): Ullrich, Alexandra; Knecht, Wolfgang; Piskur, Jure; Loffler, Monika
CORPORATE SOURCE: Institute for Physiological Chemistry, Philipps-University, Marburg, D-35033, Germany
SOURCE: FEBS Letters (2002), 529(2-3), 346-350
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mitochondrial membrane bound **dihydroorotate** dehydrogenase (DHODH; E.C. 1.3.99.11) catalyzes the fourth step of pyrimidine biosynthesis. By the present correction of a known cDNA sequence for Arabidopsis thaliana DHODH we revealed the importance of the very C-terminal part for its catalytic activity and the reason why - in contrast to mammalian and insect species - the recombinant plant flavoenzyme was unaccessible to date for in vitro characterization. Structure-activity relationship studies explained that potent inhibitors of animal DHODH do not significantly affect the plant enzyme. These difference could be exploited for a novel approach to herb or pest growth control by limitation of pyrimidine nucleotide pools.

IT **96187-53-0**, Brequinar
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cloning and characterization of **dihydroorotate** dehydrogenase (E.C. 1.3.99.11) of Arabidopsis thaliana)

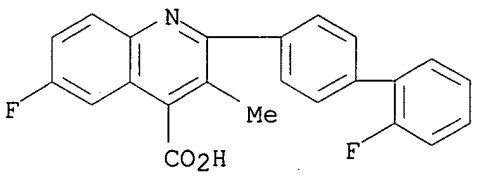
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cloning and characterization of **dihydroorotate** dehydrogenase (E.C. 1.3.99.11) of Arabidopsis thaliana)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 138:163161 CA
TITLE: In vitro and in vivo inhibition of immunoglobulin secretion by the immunosuppressive compound HR325 is reversed by exogenous uridine
AUTHOR(S): Thomson, T. A.; Spinella-Jaegle, S.; Francesconi, E.; Meakin, C.; Millet, S.; Flao, K. L.; Hidden, H.; Ruuth, E.
CORPORATE SOURCE: Immunology Domain, Hoechst Marion Roussel (now Aventis), Covingham, Swindon, UK
SOURCE: Scandinavian Journal of Immunology (2002), 56(1), 35-42
CODEN: SJIMAX; ISSN: 0300-9475
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objective was to demonstrate that the immunosuppressive agent HR325 (an inhibitor of **dihydroorotate** dehydrogenase, DHODH) inhibits Ig secretion both in vitro and in vivo and that this effect can be reversed with exogenous uridine. In vitro, Ig secretion from mouse splenocytes was induced by lipopolysaccharide (LPS) for 5 days. HR325 inhibited the secretion of IgM and IgG with IC50 values of 2.5 and 2 .mu.m, resp. Adding uridine (50 .mu.m) increased these values to 70 and 60 .mu.m, resp. Similarly, the IC50 values of another DHODH inhibitor, brequinar sodium, were also attenuated by uridine from 0.04 to 1 .mu.m for IgM, and 0.012 to 10 .mu.m for IgG. HR325 (and a structural analog A771726) inhibited LPS-induced kappa light-chain cell surface expression on 70Z/3 cells, a property also reversed by uridine. In vivo, the 2ndary anti-sheep red blood cell (SRBC) antibody response (unaffected by uridine alone) was inhibited by HR325 and brequinar with resp. ID50 values of 38 and 0.6 mg/kg per oral (p.o.). Immunosuppression with HR325 (50 mg/kg) and brequinar (1 mg/kg) was abrogated by uridine. Uridine had no effect on cyclophosphamide-induced (10 mg/kg p.o.) immunosuppression. These data are consistent with the immunosuppressive mechanism of HR325 being the result of pyrimidine depletion in vitro and in vivo.
IT **96201-88-6**, Brequinar sodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of Ig secretion by HR325 is reversed by exogenous uridine)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-

methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6,** Brequinar sodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of Ig secretion by HR325 is reversed by exogenous uridine)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 138:35133 CA
TITLE: Drosophila melanogaster **dihydroorotate** dehydrogenase: the N-terminus is important for biological function in vivo but not for catalytic properties in vitro
AUTHOR(S): Loffler, Monika; Knecht, Wolfgang; Rawls, John; Ullrich, Alexandra; Dietz, Carsten
CORPORATE SOURCE: Institute for Physiological Chemistry, Philipps-University Marburg, Marburg, D-35033, Germany
SOURCE: Insect Biochemistry and Molecular Biology (2002), 32(9), 1159-1169
CODEN: IBMBES; ISSN: 0965-1748
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

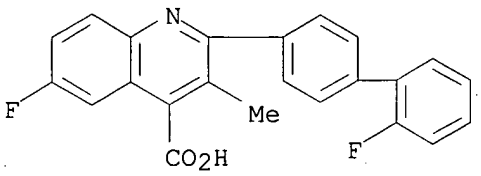
AB **Dihydroorotate** dehydrogenase (DHODH, EC 1.3.99.11), the fourth enzyme of pyrimidine de novo synthesis, is an integral flavoprotein of the inner mitochondrial membrane and is functionally connected to the respiratory chain. Here, expts. have been directed toward detg. the roles of the N-terminal sequence motifs both in enzymic properties of insect DHODH produced in vitro and the in vivo function of the protein. Full-length and three N-terminal truncated derivs. of the Drosophila melanogaster enzyme were expressed in Escherichia coli and purified. For identification on Western blots of recombinant DHODH as well as the native enzyme from flies polyclonal anti-DHODH Igs were generated and affinity-purified. The enzymic characteristics of the four versions of DHODH were very similar, indicating that the N-terminus of the enzyme does not influence its catalytic function or its susceptibility to prominent DHODH inhibitors: A77-1726, brequinar, dichloroallyl-lawsone and redoxal. Whereas the efficacy of A77-1726 and dichloroallyl-lawsone were similar with Drosophila and human DHODH, that of brequinar and redoxal differed significantly. The differences in responses of insect DHODH and the enzyme from other species may allow the design of new agents that will selectively control insect growth, due to pyrimidine nucleotide limitation. In vivo expression of the full-length and N-truncated DHODHs from engineered transgenes revealed that the truncated proteins could not support normal de novo pyrimidine biosynthesis during development of the fly (i.e., failure to complement dhod-null mutations), apparently due to

instability of the truncated proteins. It is concluded that the proper intracellular localization, directed by the N-terminal targeting and transmembrane motifs, is required for stability and subsequent proper biol. function in vivo.

IT **96187-53-0**, Brequinar
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(susceptibility of N-terminal truncated Drosophila **dihydroorotate** dehydrogenase to inhibitors)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(susceptibility of N-terminal truncated Drosophila **dihydroorotate** dehydrogenase to inhibitors)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 135:2122 CA

TITLE: Recombinant expression of N-terminal truncated mutants of the membrane bound mouse, rat and human flavoenzyme **dihydroorotate** dehydrogenase: a versatile tool to rate inhibitor effects?

AUTHOR(S): Ullrich, Alexandra; Knecht, Wolfgang; Fries, Markus; Loffler, Monika

CORPORATE SOURCE: Institut fur Physiologische Chemie, Philipps-Universitat Marburg, Marburg, D-35033, Germany

SOURCE: European Journal of Biochemistry (2001), 268(6), 1861-1868
CODEN: EJBCAI; ISSN: 0014-2956

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

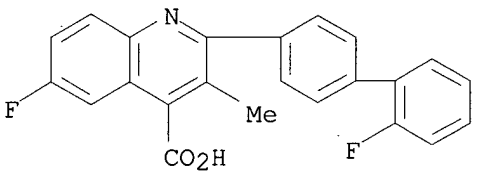
AB Mammalian **dihydroorotate** dehydrogenase, the fourth enzyme of pyrimidine de novo synthesis is an integral protein of the inner mitochondrial membrane that faces the intermembrane space and is functionally connected to the respiratory chain via ubiquinone. Here, we describe the first cloning and analyzing of the complete cDNA of mouse **dihydroorotate** dehydrogenase. Based on our recent functional expression of the full-length rat and human **dihydroorotate** dehydrogenase, here we expressed N-terminal-truncated C-terminal-histidine-tagged constructs of the mouse, rat and human enzymes in Escherichia coli. These proteins were devoid of the N-terminal bipartite sequence consisting of the mitochondrial targeting sequence and adjacent hydrophobic domain necessary for import and proper location and fixation of the enzyme in the inner mitochondrial membrane. By employing metal-chelate affinity chromatog. under native conditions, the enzymes were purified without

detergents to a specific activity of more than 100 .mu.mol.cntdot.min-1.cntdot.mg-1 at pH optimum of 8.0-8.1. Flavin analyses by UV-visible spectrometry of the native enzymes gave fairly stoichiometric ratios of 0.6-1.2 mol flavin per mol protein. The kinetic consts. of the truncated rat enzyme (Km = 11 .mu.M **dihydroorotate**; Km = 7 .mu.M ubiquinone) and human enzyme (Km = 10 .mu.M **dihydroorotate**; Km = 14 .mu.M ubiquinone) were very close to those recently reported for the full-size enzymes. The consts. for the mouse enzyme, Km = 26 .mu.M **dihydroorotate** and Km = 62 .mu.M ubiquinone, were slightly elevated in comparison to those of the other species. The three truncated enzymes were tested for their efficacy with five inhibitors of topical clin. relevance against autoimmune disorders and tumors. Whereas the presence of the N-terminus of **dihydroorotate** dehydrogenase was essentially irrelevant for the efficacy of the malononitrilamides A77-1726, MNA715 and MNA279 with the rat and human enzyme, the N-termini were found to be important for the efficacy of the dianisidine deriv. redoxal. Moreover, the complete N-terminal part of the human enzyme seemed to be of crucial importance for the "slow-binding" features of the cinchoninic acid deriv. brequinar, which was suggested to be one of the reasons for the narrow therapeutic window reported from clin. trials on its anti-proliferative and immunosuppressive action.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; recombinant N-terminal truncated mutants of mammalian **dihydroorotate** dehydrogenase and use in drug screening)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; recombinant N-terminal truncated mutants of mammalian **dihydroorotate** dehydrogenase and use in drug screening)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

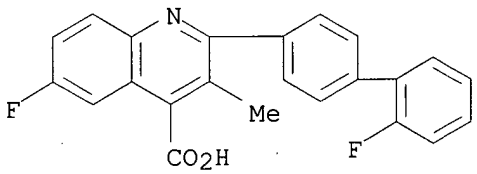
L14 ANSWER 5 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 134:248714 CA
TITLE: Multiple Inhibitor Analysis of the Brequinar and Leflunomide Binding Sites on Human **Dihydroorotate** Dehydrogenase
AUTHOR(S): McLean, Jeremy E.; Neidhardt, Edie A.; Grossman, Trudy H.; Hedstrom, Lizbeth
CORPORATE SOURCE: Program in Biophysics and Structural Biology, Brandeis University, Waltham, MA, 02454, USA
SOURCE: Biochemistry (2001), 40(7), 2194-2200
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Brequinar and the active metabolite of leflunomide, A77 1726, have been clearly shown to inhibit human **dihydroorotate** dehydrogenase (DHODH), but conflicting mechanisms for their inhibition have been reported. DHODH catalyzes the conversion of **dihydroorotate** (DHO) to orotate concurrent with the redn. of ubiquinone. This study presents data that indicates brequinar is a competitive inhibitor vs. ubiquinone; A77 1726 is noncompetitive vs. ubiquinone and both are uncompetitive vs. DHO. 2-Ph 4-quinolinecarboxylic acid (PQC), the core moiety of brequinar also shows competitive inhibition vs. ubiquinone. Multiple inhibition expts. indicate that PQC (and thus brequinar) and A77 1726 have overlapping binding sites. Both PQC and A77 1726 are also mutually exclusive with barbituric acid (a competitive inhibitor vs. DHO). In addn., the authors failed to observe brequinar binding to E.cntdot.orotate by isothermal titrn. calorimetry (ITC). These results indicate that the E.cntdot.DHO.cntdot.inhibitor and E.cntdot.orotate.cntdot.inhibitor ternary complexes do not form. The absence of these complexes is consistent with the two-site ping-pong mechanism reported for DHODH. This kinetic data suggests that recent crystal structures of human DHODH complexed with orotate and A77 1726 or brequinar may not represent the relevant physiol. binding sites for these inhibitors.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(human **dihydroorotate** dehydrogenase inhibition by brequinar, leflunomide metabolite, Ph quinolinecarboxylate, and antimycin A4)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(human **dihydroorotate** dehydrogenase inhibition by brequinar, leflunomide metabolite, Ph quinolinecarboxylate, and antimycin A4)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 132:216540 CA

TITLE: Kinetics of inhibition of human and rat **dihydroorotate** dehydrogenase by atovaquone, lawsone derivatives, brequinar sodium and polyporic acid

AUTHOR(S): Knecht, W.; Henseling, J.; Loffler, M.

CORPORATE SOURCE: Institute for Physiological Chemistry, School of Medicine, Philipps University Marburg, Marburg, D-35033, Germany

SOURCE: Chemico-Biological Interactions (2000), 124(1), 61-76
CODEN: CBINA8; ISSN: 0009-2797

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

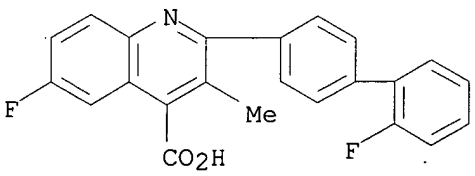
LANGUAGE: English

AB Mitochondrially-bound **dihydroorotate** dehydrogenase (EC 1.3.99.11) catalyzes the fourth sequential step in the de novo synthesis of uridine monophosphate. The enzyme has been identified as or surmised to be the pharmacol. target for isoxazol, triazine, cinchoninic acid and (naphtho)quinone derivs., which exerted antiproliferative, immunosuppressive, and antiparasitic effects. Despite this broad spectrum of biol. and clin. relevance, there have been no comparative studies on drug-**dihydroorotate** dehydrogenase interactions. The authors describe a study of the inhibition of the purified recombinant human and rat **dihydroorotate** dehydrogenase by ten compds. 1,4-Naphthoquinone, 5,8-dihydroxynaphthoquinone and the natural compds. juglon, plumbagin and polyporic acid (quinone deriv.) were found to function as alternative electron acceptors with 10-30% of control enzyme activity. The human and rat enzyme activity was decreased by 50% by the natural compd. lawsone (500 and 49 .mu.M, resp.) and by the derivs. dichloroallyl-lawsone (67 and 10 nM), lapachol (618 and 61 nM) and atovaquone (15 .mu.M and 698 nM). With respect to the quinone co-substrate of the **dihydroorotate** dehydrogenase, atovaquone (Kic=2.7 .mu.M) and dichloroallyl-lawsone (Kic=9.8 nM) were shown to be competitive inhibitors of human **dihydroorotate** dehydrogenase. Atovaquone (Kic=60 nM) was also a competitive inhibitor of the rat enzyme. Dichloroallyl-lawsone was a time-dependent inhibitor of the rat enzyme, with the lowest inhibition const. (Ki*=0.77 nM) detd. so far for mammalian **dihydroorotate** dehydrogenases. Another inhibitor, brequinar was previously reported to be a slow-binding inhibitor of the human **dihydroorotate** dehydrogenase [W. Knecht, M. Loffler, Species-related inhibition of human and rat **dihydroorotate** dehydrogenase by immunosuppressive isoxazol and cinchoninic acid derivs., Biochem. pharmacol. 56 (1998) 1259-1264]. The slow binding features of this potent inhibitor (Ki*=1.8 nM) with the human enzyme, were verified and seen to be one of the reasons for the narrow therapeutic window (efficacy vs. toxicity) reported from clin. trials on its antiproliferative and immunosuppressive action. With respect to the substrate **dihydroorotate**, atovaquone was an uncompetitive inhibitor of human **dihydroorotate** dehydrogenase (Kiu=11.6 .mu.M) and a non-competitive inhibitor of the rat enzyme (Kiu=905/Kic=1012 nM). Polyporic acid (1.5 mM) , a natural quinone from fungi, influenced the activity of the human enzyme only slightly; the activity of the rat enzyme was decreased by 30%.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(kinetics of inhibition of human and rat **dihydroorotate** dehydrogenase by atovaquone and lawsone derivs. and brequinar sodium and polyporic acid in relation to structure)

RN 96201-88-6 CA

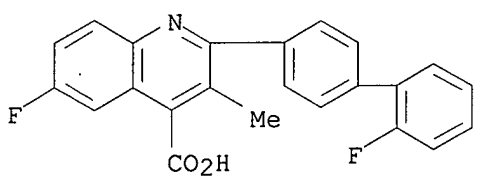
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



Na

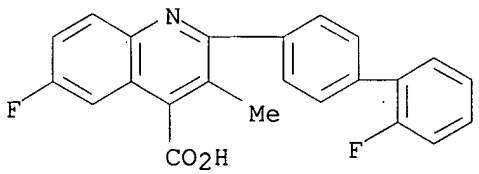
IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(kinetics of inhibition of human and rat **dihydroorotate** dehydrogenase by atovaquone and lawsone derivs. and brequinar sodium and polyporic acid in relation to structure)
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 132:204810 CA
TITLE: Structures of human **dihydroorotate** dehydrogenase in complex with antiproliferative agents
AUTHOR(S): Liu, Shenping; Neidhardt, Edie A.; Grossman, Trudy H.; Ocain, Tim; Clardy, Jon
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY, 14853-1301, USA
SOURCE: Structure (London) (2000), 8(1), 25-33
CODEN: STRUE6; ISSN: 0969-2126
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Dihydroorotate** dehydrogenase (DHODH) catalyzes the fourth committed step in the de novo biosynthesis of pyrimidines. As rapidly proliferating human T cells have an exceptional requirement for de novo pyrimidine biosynthesis, small mol. DHODH inhibitors constitute an attractive therapeutic approach to autoimmune diseases, immunosuppression, and cancer. Neither the structure of human DHODH nor any member of its family was known. The high-resoln. crystal structures of human DHODH in complex with two different inhibitors have been solved. The initial set of phases was obtained using multiwavelength anomalous diffraction phasing with selenomethionine-contg. DHODH. The structures have been refined to crystallog. R factors of 16.8% and 16.2% at resolns. of 1.6.ANG. and 1.8.ANG. for inhibitors related to brequinar and leflunomide, resp. Human DHODH has two domains: an .alpha./.beta.-barrel domain contg. the active site and an .alpha.-helical domain that forms the opening of a tunnel leading to the active site. Both inhibitors share a common binding site in this tunnel, and differences in the binding region govern drug sensitivity or resistance. The active site of human DHODH is generally similar to that of the previously reported bacterial active site. The greatest differences are that the catalytic base removing the proton from **dihydroorotate** is a serine rather than a cysteine, and that packing of the FMN in its binding site is tighter.
IT **96187-53-0D**, Brequinar, analog, complexes with **dihydroorotate** dehydrogenase
RL: PRP (Properties)
(structures of human **dihydroorotate** dehydrogenase in complex with antiproliferative agents)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0D**, Brequinar, analog, complexes with **dihydroorotate** dehydrogenase
RL: PRP (Properties)
(structures of human **dihydroorotate** dehydrogenase in complex with antiproliferative agents)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 131:331684 CA
TITLE: Simultaneous separation by high-performance liquid chromatography of carbamoyl aspartate, carbamoyl phosphate and dihydroorotic acid
AUTHOR(S): Fairbanks, Lynette D.; Carrey, Elizabeth A.; Ruckemann, Katarzyna; Swaminathan, Ramasamyiyer; Kirschbaum, Bernhard; Simmonds, H. Anne
CORPORATE SOURCE: London Bridge, Thomas Guy House, Purine Research Laboratory, GKT Guy's Hospital, London, SE1 9RT, UK
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1999), 732(2), 487-493
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Leflunomide is an immunomodulatory drug which acts by inhibiting dihydroorotic acid dehydrogenase, the fourth enzyme of the pyrimidine biosynthesis pathway. Reversed-phase HPLC was used to demonstrate that the principal metabolite in mitogen-stimulated human T-lymphocytes incubated with leflunomide or brequinar was not dihydroorotic acid, but carbamoyl aspartate. Identification involved prepn. of [14C]carbamoyl aspartate from [14C]aspartic acid and mammalian aspartate transcarbamoylase. Accumulation of carbamoyl aspartate indicated that under these conditions the equil. const. for dihydroorotase favors the reverse reaction. The HPLC method allows simultaneous sepn. of the intermediates in the de novo pyrimidine pathway (carbamoyl aspartate, carbamoyl phosphate, dihydroorotic acid, orotic acid, orotidine).
IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(carbamoyl aspartate, carbamoyl phosphate and dihydroorotic acid simultaneous detn. by HPLC in T lymphocytes treated with leflunomide or brequinar)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(carbamoyl aspartate, carbamoyl phosphate and dihydroorotic acid simultaneous detn. by HPLC in T lymphocytes treated with leflunomide or

brequinar)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 130:62844 CA
TITLE: Species-related inhibition of human and rat **dihydroorotate** dehydrogenase by immunosuppressive isoxazol and cinchoninic acid derivatives
AUTHOR(S): Knecht, Wolfgang; Loffler, Monika
CORPORATE SOURCE: INSTITUTE FOR PHYSIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, PHILIPPS-UNIVERSITY, MARBURG, D-35033, Germany
SOURCE: Biochemical Pharmacology (1998), 56(9), 1259-1264
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

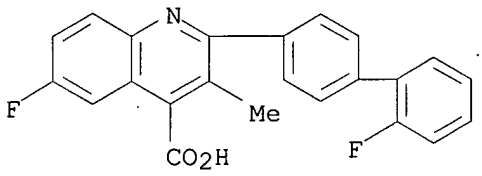
AB The isoxazol leflunomide (N-(4-trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide) and its active metabolite A77-1726 (N-(4-trifluoromethyl)-phenyl-2-cyano-3-hydroxy-crotonic acidamide) are promising disease-modifying antirheumatic drugs now in clin. trials. The malononitrilamides MNA279 (2-cyano-3-cyclopropyl-3-oxo-(4-cyanophenyl)propionamide) MNA715 (N-(4-trifluoromethyl)-phenyl-2-cyano-3-hydroxy-hept-2-en-6-in-carboxylic acidamide) and HR325 (1(3-methyl-4-trifluoromethylphenyl-carbamoyl)-2-cyclopropyl-2-oxo-propionitrile) were shown to block rejection after allograft and xenograft transplantation in animals. Brequinar and other cinchoninic acid derivs. have also been evaluated as immunosuppressive agents. A77-1726, HR325 and brequinar have been shown to have strong inhibitory effects on mitochondrial **dihydroorotate** dehydrogenase [E.C. 1.3.99.11], the fourth enzyme of pyrimidine de novo synthesis, with concomitant redn. of pyrimidine nucleotide pools. Pyrimidine nucleotides are essential for normal immune cell functions. Because most investigations had been carried out with cells, cell homogenates or mitochondrial fractions, it was the rationale of the present study to differentiate, under standardized conditions, the effect of leflunomide, A77-1726, MNA279, MNA715, HR 325 and brequinar on the recombinant rat and human enzymes, which were purified in our lab. Whereas leflunomide was a relatively weak inhibitor of the rat (IC50 = 6.3 .mu.M) and human (IC50 = 98 .mu.M) **dihydroorotate** dehydrogenase, the influence of A77-1726, MNA 279, MNA715 and HR325 was of comparable efficacy for either the rat (range of IC50, 19-53 nM) or the human enzyme (range of IC50, 0.5-2.3 .mu.M). From the IC50 values, it was deduced that brequinar was a more potent inhibitor of the human **dihydroorotate** dehydrogenase activity (IC50 = 10 nM) than of the rat enzyme (IC50 = 367 nM). The rat enzyme was influenced by all isoxazol derivs. to a greater extent (IC50 = 19 nM A77-1726) than the human enzyme (IC50 = 1.1 .mu.M A77-1726). These results may provide a plausible explanation for the findings of other labs. with cultured cell lines and lymphocytes: in comparison to cells derived from human tissues, rat and other rodent cells were more susceptible to the isoxazol derivs. and less susceptible to brequinar. Our detailed kinetic investigations of the bisubstrate reaction catalyzed by rat **dihydroorotate** dehydrogenase revealed a noncompetitive type of inhibition by A77-1726 with respect to the substrate **dihydroorotate** and the cosubstrates ubiquinone or decylubiquinone. For brequinar, the inhibition was noncompetitive with respect to the substrate **dihydroorotate**, whereas with the quinone it was found to follow the "mixed typed" inhibition. In addn., brequinar acted as a "slow-binding" inhibitor of

the human **dihydroorotate** dehydrogenase, a feature that might be of consequence for the reversibility of the reaction with the target.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(inhibitor; species-related inhibition of human and rat **dihydroorotate** dehydrogenase by immunosuppressive isoxazol and cinchoninic acid derivs.)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(inhibitor; species-related inhibition of human and rat **dihydroorotate** dehydrogenase by immunosuppressive isoxazol and cinchoninic acid derivs.)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 10 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 130:20319 CA

TITLE: Structural and functional comparison of agents interfering with **dihydroorotate**, succinate and NADH oxidation of rat liver mitochondria

AUTHOR(S): Jockel, Johannes; Wendt, Bernd; Loffler, Monika

CORPORATE SOURCE: Institute for Physiological Chemistry, School of Medicine, Philipps-University, Marburg, D-35033, Germany

SOURCE: Biochemical Pharmacology (1998), 56(8), 1053-1060
CODEN: BCPCA6; ISSN: 0006-2952

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

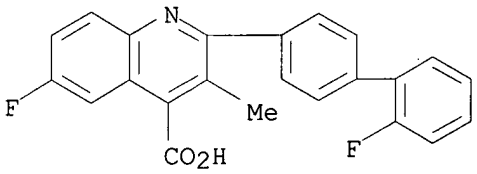
AB Mitochondrially bound **dihydroorotate** dehydrogenase (EC 1.3.99.11) catalyzes the fourth sequential step in the de novo synthesis of uridine monophosphate; this enzyme uses ubiquinone as the proximal and cytochrome oxidase as is the ultimate electron transfer system. Here, seven compds. with proven antiproliferative activity and in vitro antipyrimidine effects were investigated with isolated functional mitochondria of rat tissues in order to differentiate their anti-**dihydroorotate** dehydrogenase potency vs. putative effects on the respiratory chain enzymes. Ten .mu.M of brequinar sodium, the leflunomide derivs. A77-1726, [2-cyano-3-cyclopropyl-3-hydroxy-enoic acid (4-trifluoromethyl)-amide], MNA 279, (2-cyano-N-(4-cyanophenyl-3-cyclopropyl-3-oxo-propanamide), MNA715 (2-cyano-3-hydroxy-N-4-(trifluoromethyl)-phenyl-6-heptanamide), HR325 (2-cyano-3-cyclopropyl-3-hydroxy-N-[3'-methyl-4'-(trifluoromethyl)phenyl]-propenamide), and the diazine toltrazuril completely inhibited the **dihydroorotate** -induced oxygen consumption of liver mitochondria. Succinate and NADH oxidn. were found to be influenced only at elevated drug concn. (100

.mu.M), with the exception of HR325, 10 .mu.M of which caused a 70% inhibition of NADH and 50% inhibition of succinate oxidn. This was comparable to the effects of toltrazuril, which caused an approx. 75% inhibition of NADH oxidn. Ciprofloxacin was shown here to have only marginal effects on the redox activities of the inner mitochondrial membrane. This differentiation of drug effects on mitochondrial functions will contribute to a better understanding of the in vivo pharmacol. activity of these drugs, which are presently in clin. trials because of their immunosuppressive, cytostatic or anti-parasitic activity. A comparison of the influence of A77-1726, HR325, brequinar and 2,4-dinitrophenol on energetically coupled rat liver mitochondria revealed only a weak uncoupling potential of A77-1726 and brequinar. In addn., a modeling study was raised to search for common spatial arrangements of functional groups essential for binding of inhibitors to **dihydroorotate** dehydrogenase. From the structural comparison of different metabolites and inhibitors of pyrimidine metab., a 6-point model was obtained by conformational anal. for the drugs tested on mitochondrial functions, pharmacophoric perception and mapping. We propose our model in combination with kinetic data for a rational design of highly specific inhibitors of **dihydroorotate** dehydrogenase.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structural and functional comparison of agents interfering with **dihydroorotate**, succinate and NADH oxidn. of rat liver mitochondria)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium **131745-25-0**, C1306293
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structural and functional comparison of agents interfering with **dihydroorotate**, succinate and NADH oxidn. of rat liver mitochondria)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

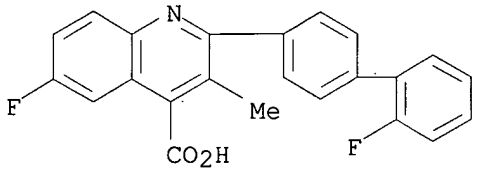
L14 ANSWER 11 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 129:312551 CA
TITLE: **Dihydroorotate** dehydrogenase: profile of a novel target for antiproliferative and immunosuppressive drugs
AUTHOR(S): Loffler, Monika; Grein, Klaus; Knecht, Wolfgang; Klein, Astrid; Bergjohann, Ute

CORPORATE SOURCE: Institute Physiological Chemistry, School Medicine, Philipps-Univ., Marburg, D-35033, Germany
SOURCE: Advances in Experimental Medicine and Biology (1998), 431(Purine and Pyrimidine Metabolism in Man IX, 1998), 507-513
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Methods from our lab. could provide useful anal. tools to detect and follow the effect of continuous drug exposure on the DHOdehase protein expression in cells and tissue. This may be of vital importance in view of putative development of drug resistance.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**dihydroorotate** dehydrogenase, profile of a novel target for antiproliferative and immunosuppressive drugs)

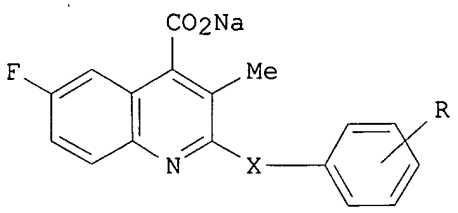
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



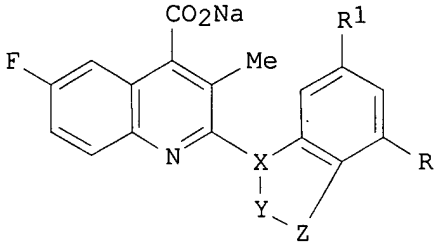
IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**dihydroorotate** dehydrogenase, profile of a novel target for antiproliferative and immunosuppressive drugs)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 12 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 129:202848 CA
TITLE: Heteroatom- and carbon-linked biphenyl analogs of Brequinar as immunosuppressive agents
AUTHOR(S): Batt, Douglas G.; Petraitis, Joseph J.; Sherk, Susan R.; Copeland, Robert A.; Dowling, Randine L.; Taylor, Tracy L.; Jones, Elizabeth A.; Magolda, Ronald L.; Jaffee, Bruce D.
CORPORATE SOURCE: The DuPont Merck Pharmaceutical Company, Wilmington, DE, 19880-0500, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1998), 8(13), 1745-1750
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



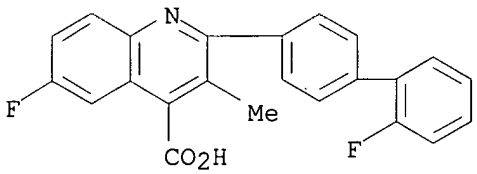
II

AB Structure-activity relationships were explored for analogs I [X = O, Nh, NMe, NAc, OCH2; R = H, 3-Ph, 4-Ph] and II [XYŻ = NCH2CH2, NCH:CH, NCH:N, CH:CHNH, CH:CHNMe, CH:CHCH:CH; R = Ph, 2-FC6H4, 2-MeC6H4, 2-MeOC6H4, 2-CF3C6H4, 3-MeOC6H4; R1 = H, F, OMe] of Brequinar having a linking atom between the 2-biphenyl substituent and the quinoline ring. Activities as inhibitors of **dihydroorotate** dehydrogenase and the mixed lymphocyte reaction were related to the overall shape and lipophilicity of the 2-substituent.

IT **96187-53-0DP**, Brequinar, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of biphenyl analogs of Brequinar as immunosuppressive agents)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0DP**, Brequinar, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of biphenyl analogs of Brequinar as immunosuppressive agents)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 128:265737 CA

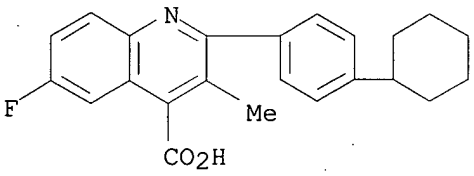
TITLE: **Dihydroorotate** dehydrogenase inhibitors: quantitative structure-activity relationship analysis

AUTHOR(S): Ren, Shijun; Wu, Sharon K.; Lien, Eric J.
CORPORATE SOURCE: School of Pharm., Univ. Southern California, Los Angales, CA, USA
SOURCE: Pharmaceutical Research (1998), 15(2), 286-295
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The main purpose of this study is to analyze the QSAR of 2 series of **dihydroorotate** dehydrogenase inhibitors (leflunomide and quinolinecarboxylic acid analogs), and to det. the structural requirements for optimum activity of these analogs. A new CQSAR program was used in deriving regression equations and calcg. the octanol/water partition coeff. and the molar refractivity values. The mol. modeling was performed by using the HyperChem program. Statistically significant correlations were obtained using a combination of 3-4 parameters. The structural requirements for optimum activity and crit. regions for the inhibitory activity of **dihydroorotate** dehydrogenase were identified. The QSAR anal. demonstrated that 2 series of **dihydroorotate** dehydrogenase inhibitors may bind to different binding sites on the enzyme. These results provide a better understanding of **dihydroorotate** dehydrogenase inhibitor-enzyme interactions, and may be useful for further modification and improvement of inhibitors of this important enzyme.

IT **96187-26-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(QSAR anal. of **dihydroorotate** dehydrogenase inhibitors)

RN 96187-26-7 CA
CN 4-Quinolinecarboxylic acid, 2-(4-cyclohexylphenyl)-6-fluoro-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-26-7 96187-27-8 96187-30-3**
96187-31-4 96187-35-8 96187-37-0
96187-53-0 96187-55-2 96187-56-3
96187-60-9 96187-62-1 96187-63-2
96187-64-3 96201-24-0 96201-28-4
96201-40-0 96201-42-2 96201-45-5
96201-46-6 96201-48-8 96201-63-7
96202-55-0 130507-51-6 130507-59-4
130507-60-7 130507-61-8 130507-62-9
130507-63-0 130507-64-1 130507-65-2
130507-66-3 130507-67-4 130507-68-5
205682-29-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(QSAR anal. of **dihydroorotate** dehydrogenase inhibitors)

IT **96201-88-6D**, Brequinar sodium, analogs
RL: PRP (Properties)
(QSAR anal. of **dihydroorotate** dehydrogenase inhibitors)

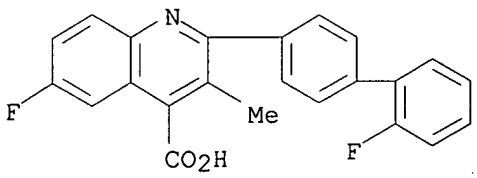
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 14 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 128:188448 CA
TITLE: In vitro and in vivo mechanisms of action of the antiproliferative and immunosuppressive agent, brequinar sodium
AUTHOR(S): Xu, Xiulong; Williams, James W.; Shen, Jikun; Gong, Haihua; Yin, Deng-Ping; Blinder, Leonard; Elder, Robert T.; Sankary, Howard; Finnegan, Alison; Chong, Anita S.-F.
CORPORATE SOURCE: Departments of General Surgery and Immunology/Microbiology and Section of Rheumatology, Dep. of Internal Medicine, Rush Medical College, Chicago, IL, 60612, USA
SOURCE: Journal of Immunology (1998), 160(2), 846-853
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Intracellular pyrimidine nucleotides (PyN) can be synthesized de novo from glutamine, CO2, and ATP, or they can be salvaged from performed pyrimidine nucleosides. The antiproliferative and immunosuppressive activities of brequinar sodium (BQR) are thought to be due to the inhibition of the activity of **dihydroorotate** dehydrogenase, which results in a suppression of de novo pyrimidine synthesis. Here we describe the effects of the pyrimidine nucleoside, uridine, on the antiproliferative and immunosuppressive activities of BQR. In vitro redn. of PyN levels in Con A-stimulated t cells and inhibition of cell proliferation by low concns. of BQR (.ltoreq.65 .mu.M) are reversed by uridine. However, uridine is unable to reverse the effects of high concns. of BQR (.gtoreq.65 .mu.M). The ability of BQR to induce anemia in BALB/c mice is prevented by the coadministration of uridine. In contrast, the immunosuppressive activity of BQR is unaffected by similar doses of uridine. PyN levels in the bone marrow, but not in the spleen, are depressed in mice treated with BQR. These observations suggest that the induction of anemia by BQR is due to depletion of intracellular PyN in hemopoietic stem cells located in the bone marrow. They also suggest that the mechanism of immunosuppression by BQR may be only marginally dependent on depletion of intracellular PyN in lymphocytes located in the periphery. We report a novel activity of BQR: inhibition of tyrosine phosphorylation, and hypothesize that the immunosuppressive activity may be due, in part, to this unsuspected ability of BQR to inhibit tyrosine phosphorylation in lymphocytes.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative and immunosuppressive agent brequinar sodium mechanisms of action)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses).
(antiproliferative and immunosuppressive agent brequinar sodium mechanisms of action)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 128:70532 CA
TITLE: Control of lymphoproliferative and autoimmune disease in MRL-lpr/lpr mice by brequinar sodium: mechanisms of action
AUTHOR(S): Xu, Xiulong; Gong, Haihua; Blinder, Leonard; Shen, Jikun; Williams, James W.; Chong, Anita S. -F.
CORPORATE SOURCE: Department of General Surgery, Rush Presbyterian St. Luke's Medical Center, Chicago, IL, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 283(2), 869-875
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

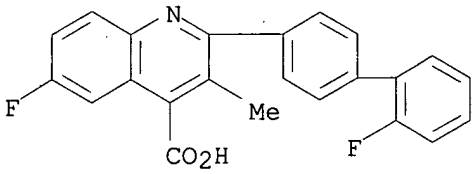
AB Brequinar sodium (BQR) was originally developed as an antitumor drug and subsequently as an immunosuppressant for controlling transplant rejection. It has been widely accepted that the antitumor and immunosuppressive activities of BQR are dependent on its ability to inhibit the enzymic activity of **dihydroorotate** dehydrogenase, the fourth enzyme in the de novo pyrimidine synthesis pathway. Recently, we discovered that BQR has the ability to inhibit protein tyrosine phosphorylation in anti-CD3-stimulated murine T lymphocytes and to inhibit the activity of src-related protein tyrosine kinases, p56lck and p59fyn. We examd. the in vivo activities of BQR in MRL-lpr/lpr mice. We report that the dose of BQR (10 mg/kg/day) that induced anemia, controlled lymphadenopathy and inhibited autoantibody prodn., also selectively reduced the pyrimidine nucleotide levels in the bone marrow and in the lymph nodes. Coadministration of uridine (1000 mg/kg/day) with BQR completely normalized pyrimidine nucleotide levels in the bone marrow and lymph nodes, and prevented BQR-induced anemia. However, coadministration of uridine with BQR only partially reversed the anti-proliferative effects of BQR, and did not antagonize the inhibitory effect of BQR on autoantibody prodn. Finally, we report that BQR markedly reduced protein tyrosine phosphorylation in lymph nodes of MRL-lpr/lpr mice. These results collectively suggest that the control of lymphadenopathy and autoantibody prodn. in MRL-lpr/lpr mice by BQR is only partially dependent on inhibition of pyrimidine nucleotide synthesis, and suggest a crit. role

for in vivo inhibition of protein tyrosine phosphorylation.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(control of lymphoproliferative and autoimmune disease in MRL-lpr/lpr mice by brequinar sodium and mechanisms of action)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(control of lymphoproliferative and autoimmune disease in MRL-lpr/lpr mice by brequinar sodium and mechanisms of action)

L14 ANSWER 16 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 127:341515 CA

TITLE: Immunosuppressive effect on alloimmune responses of new immunosuppressant, KF20444

AUTHOR(S): Ito, Toshinori; Kamilke, Wataru; Ohkawa, Atsushi; Nozaki, Shunichi; Sawai, Tsutomu; Nakajima, Hiroshi; Sato, Soichiro; Matsuda, Hikaru

CORPORATE SOURCE: First Department of Surgery, Osaka University Medical School, Osaka, 565, Japan

SOURCE: Organ Biology (1997), 4(2), 43-48
CODEN: ORBIF3; ISSN: 1340-5152

PUBLISHER: Nippon Zoki Hozon Seibutsu Igakkai

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

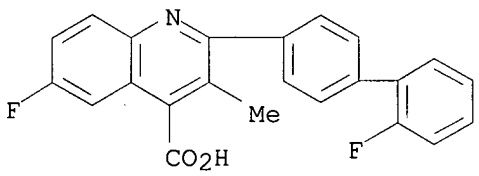
AB KF20444 (KF) is a new immunosuppressive agent that inhibits **dihydroorotate** dehydrogenase (DHO-DH) and interfaces with de novo synthesis of pyrimidine, which mechanism is similar to that of Brequinar sodium (BQR). It has been recently demonstrated that KF was highly effective for prevention and treatment of adjuvant arthritis models of rodents. In the present study, we have examd. the effectiveness of KF on the suppression of MLR and graft survivals of rat heart transplantation, comparing to those of BQR. Spleens were harvested from naive or sensitized LEW (RT1) rats which fully allogenic BUF (RT1) heart grafts were already rejected. Naive or sensitized purified 2x105 LEW splenic T cells were mixed with 20 Gy irradiated 4.times.105 BUF stimulator cells for 4 days at 37.degree. in 5% CO2. Either KF or BQR ranging from final concn. of 0.03 to 2 .mu.g/mL was added at the beginning of or after 48 h of incubation in MLR. KF or BQR was administered at the dosage of 1 to 4 mg/kg by gavage daily from day 0 to +6 after transplantation. The results of MLR demonstrated that KF could suppress approx. 10 times stronger at

any point of concns. than BQR. The concns. of KF and BQR required for 50% inhibition (LC50) in MLR using naive responder T cells were 0.04 .mu.g/mL and 0.3 .mu.g/mL, resp. Even after 48 h of incubation, KF could significantly inhibit the MLR proliferative response. Also in MLR using sensitized T cells, KF could more efficiently inhibit the proliferative response compared to BQR. A short course treatment of KF (1mg/kg .times. 7 days) could significantly prolong mean graft survival from 8.2 to > 100 days, where that of BQR was only 16.7 days. In case of rescue therapy, cardiac grafts were well preserved in their function during the administration of KF, but rejected in an acute fashion after the cessation. These results suggested that KF was a more potent immunosuppressant which inhibits the sensitization phase as well as the initiation phase of MLR than BQR.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressive effect on alloimmune responses of new immunosuppressant, KF20444)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressive effect on alloimmune responses of new immunosuppressant, KF20444)

L14 ANSWER 17 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 127:257287 CA

TITLE: Histidine to alanine mutants of human **dihydroorotate** dehydrogenase. Identification of a brequinar-resistant mutant enzyme

AUTHOR(S): Davis, June P.; Copeland, Robert A.

CORPORATE SOURCE: INFLAMMATORY DISEASES RESEARCH, THE DUPONT MERCK RESEARCH LABORATORIES, WILMINGTON, DE, 19880-0400, USA

SOURCE: Biochemical Pharmacology (1997), 54(4), 459-465
CODEN: BCPCA6; ISSN: 0006-2952

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

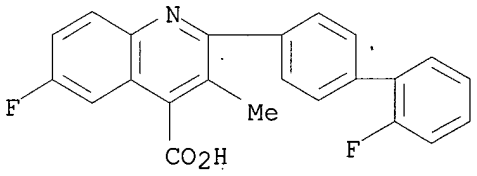
AB **Dihydroorotate** dehydrogenase (DHODase) is the rate-limiting enzyme of the mammalian de novo pyrimidine biosynthesis pathway, and is the mol. target of the antiproliferative, immunosuppressive compd. brequinar sodium (BQR). The authors have shown previously that the activity of the recombinant human enzyme displays pH and

diethylpyrocarbonate sensitivities that implicate a crit. role for one or more histidine residues in catalysis [Copeland et al., Arch Biochem Biophys 323: 79-86, 1995.]. Here the authors report the results of alanine scanning mutagenesis for each of the 8 histidine residues of the recombinant human enzyme. In most cases, the replacement of histidine by alanine had little effect on the Km values of the two substrates, **dihydroorotate** and ubiquinone, or on the overall kcat of the enzymic reaction. Replacement of H71, H129, and H364 by alanine, however, completely abolished enzymic activity. The loss of activity for the H71A mutant was unexpected, since this residue is not conserved in the homologous rat enzyme; in the rodent enzyme this residue is an asparagine. Replacement of H71 by asparagine in the human enzyme led to a full recovery of enzymic activity, indicating that a histidine is not required at this position. Replacement of H26 by alanine led to about a 10-fold redn. in catalytic activity relative to the wild-type enzyme, with no significant perturbation of the substrate Km values. This mutant was, however, at least 167-fold less sensitive to inhibition by the noncompetitive inhibitor BQR. While the wild-type and other mutant enzymes displayed IC50 values for BQR inhibition between 6 and 10 nM, the H26A mutant was inhibited less than 25% at concns. of BQR as high as 150 nM. These data suggest that H26 plays an important role in BQR binding to the enzyme.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(histidine to alanine mutants of human **dihydroorotate** dehydrogenase and identification of a brequinar-resistant mutant enzyme)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(histidine to alanine mutants of human **dihydroorotate** dehydrogenase and identification of a brequinar-resistant mutant enzyme)

L14 ANSWER 18 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 126:272034 CA
TITLE: In vitro and in vivo effects of leflunomide, brequinar, and cyclosporine on pyrimidine biosynthesis
AUTHOR(S): Silva, H. T., Jr.; Cao, W.; Shorthouse, R. A.; Loffler, M.; Morris, R. E.
CORPORATE SOURCE: Department of Cardiothoracic Surgery, Transplantation Immunology, Stanford University School of Medicine, Stanford, CA, 94305-5247, USA

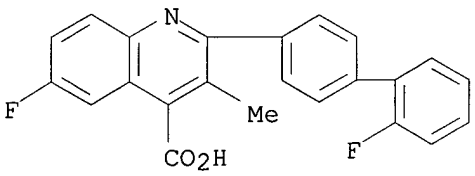
SOURCE: Transplantation Proceedings (1997), 29(1/2), 1292-1293
CODEN: TRPPA8; ISSN: 0041-1345
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Uridine and orotate antagonized in vitro and in vivo antiproliferative (mitogen-stimulated lymphocyte proliferation) effects of leflunomide in a similar fashion as the antagonism obsd. of brequinar, a known inhibitor of **dihydroorotate** dehydrogenase, but not cyclosporin A anti-proliferative effects. Furthermore, leflunomide completely inhibited **dihydroorotate** dehydrogenase activity of lymphocytes infiltrating heart allografts in mice. Therefore, an important mechanism of the antiproliferative effect of leflunomide in vivo appears to be the inhibition of **dihydroorotate** dehydrogenase, leading to reduced de novo pyrimidine biosynthesis.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of leflunomide, brequinar, and cyclosporine on pyrimidine biosynthesis)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of leflunomide, brequinar, and cyclosporine on pyrimidine biosynthesis)

L14 ANSWER 19 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 125:104439 CA

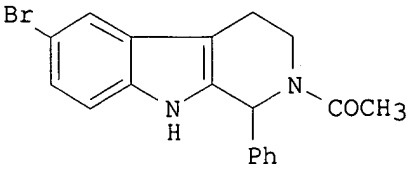
TITLE: Identification of a novel inhibitor (NSC 665564) of **dihydroorotate** dehydrogenase with a potency equivalent to brequinar

AUTHOR(S): Cleaveland, Emily S.; Zaharevitz, Daniel W.; Kelley, James A.; Paull, Kenneth; Cooney, David A.; Ford, Harry, Jr.

CORPORATE SOURCE: Lab. Med. Chem., Div. Basic Sci., Natl. Inst. Health, Bethesda, MD, 20892, USA

SOURCE: Biochemical and Biophysical Research Communications (1996), 223(3), 654-659
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

GI



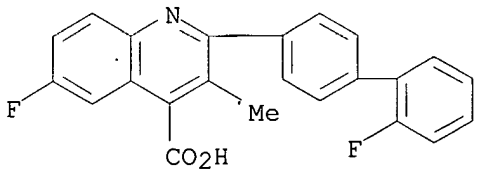
I

AB A novel inhibitor of **dihydroorotate** dehydrogenase (DHO-DH) has been discovered using data from the National Cancer Institute's in vitro drug screen. Upon anal. of cytotoxicity results from the sixty tumor cell lines used in this screen, the COMPARE program predicted that NSC 665564 (I) was likely to have the same mechanism of inhibition as brequinar, a known potent inhibitor of DHO-DH. We validated this prediction exptl. using MOLT-4 lymphoblast and found the IC50 of brequinar (0.5 .mu.M) and I (0.3 .mu.M) were comparable and that this induced cytotoxicity was reversed by either uridine or cytidine. The enzyme target of I was shown to be identical to that of brequinar when incubation with each drug followed by a 1 h pulse with sodium [14C]bicarbonate resulted in cellular accumulation of [14C]N-carbamyl-L-aspartic acid and [14C]L-dihydroorotic acid, with concurrent marked depletion of CTP and UTP. The Ki's for I and brequinar were 0.14 and 0.24 .mu.M, resp., when partially purified MOLT-4 mitochondria (the site of DHO-DH) were used. These results show that mechanistic predictions obtained using correlations from the COMPARE algorithm are independent of structure since the structure of I is dissimilar to that of other established DHO-DH inhibitors.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NSC 665564 as inhibitor of **dihydroorotate** dehydrogenase with potency equiv. to brequinar and tumor cytotoxic effects)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NSC 665564 as inhibitor of **dihydroorotate** dehydrogenase with potency equiv. to brequinar and tumor cytotoxic effects)

L14 ANSWER 20 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 124:250183 CA
TITLE: Effects of the novel immunosuppressant brequinar on hepatic UDP-glucuronic acid levels and UDP-glucuronyltransferase activities in the rat
AUTHOR(S): Diamond, Sharon; Christ, David D.
CORPORATE SOURCE: Drug Metabolism Pharmacokinetics Section, DuPont Merck

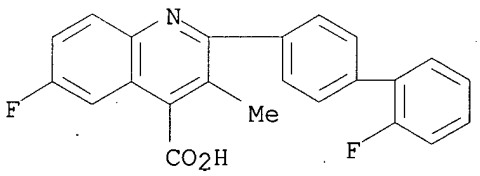
Pharmaceutical Co., USA
SOURCE: Drug Metabolism and Disposition (1996), 24(3), 375-6
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB BQR [2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-6-fluoro-4-quinolinecarboxylic acid] is a novel immunosuppressant that inhibits **dihydroorotate** dehydrogenase, the fourth enzyme in the pathway leading to the formation of UMP and thus de novo pyrimidine synthesis. Decreased total hepatic uridine nucleotides, measured after hydrolysis to UMP, have been obsd. by some after BQR treatment, whereas others have obsd. a relatively small depletion of pyrimidine nucleotides in murine livers after treatment with BQR. The possibility that decreased levels of UMP after BQR dosing may result in impaired xenobiotic glucuronidation, by lowering hepatic UDP-glucuronic acid, was therefore investigated. Moreover, glucuronidation is a major pathway of BQR metab. in rats. In addn. to intracellular levels of UDP-glucuronic acid, glucuronidation is dependent on the activity of the UDP-glucuronyltransferases (UDPGTs); therefore, the effect of BQR on the glucuronidation of selective substrates for isoenzymes of the UDPGT1 and UDPGT2 families was evaluated. These studies were designed to det. the potential for BQR to affect glucuronidation by decreasing co-substrate levels or inhibiting UDPGT isoenzymes directly.

IT **96187-53-0**, Brequinar
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(brequinar effect on hepatic UDP-glucuronic acid levels and UDP-glucuronyltransferase activity)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(brequinar effect on hepatic UDP-glucuronic acid levels and UDP-glucuronyltransferase activity)

L14 ANSWER 21 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 124:21025 CA
TITLE: Immunosuppressive structure-activity relationships of Brequinar and related cinchoninic acid derivatives
AUTHOR(S): Batt, Douglas G.; Copland, Robert A.; Dowling, Randine L.; Gardner, Tracy L.; Jones, Elizabeth A.; Orwat, Michael J.; Pinto, Donald J.; Pitts, William J.; Magolda, Ronald L.; Jaffee, Bruce D.
CORPORATE SOURCE: Inflammatory Disease Res., DuPont Merck Pharmaceutical Co., Wilmington, DE, 19880-0353, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1995),

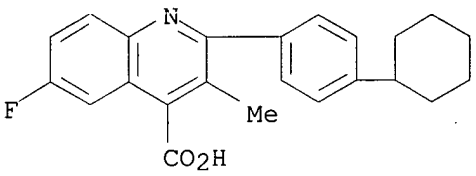
5(14), 1549-54
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The immunosuppressive structure-activity relationships of substituted cinchoninic acid derivs. related to Brequinar (I) were explored. Activities as inhibitors of **dihydroorotate** dehydrogenase and the mixed lymphocyte reaction were related to benzo-ring substitution, replacement of the benzo-ring by heterocycles, and variation in the 2-biphenyl, 3-Me, and 4-carboxy groups.

IT **96187-26-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(immunosuppressive structure-activity relationships of Brequinar and related cinchoninic acid derivs.)

RN 96187-26-7 CA

CN 4-Quinolinecarboxylic acid, 2-(4-cyclohexylphenyl)-6-fluoro-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-26-7P 96187-27-8P 96187-39-2P**
96187-43-8P 96187-44-9P 96187-53-0DP,
Brequinar, derivs. **96187-61-0P 96187-73-4P**
96201-22-8P 96201-28-4P 96201-48-8P
96201-52-4P 96201-73-9P 96201-90-0P
96201-91-1P 96227-04-2P 115329-88-9P
122262-72-0P 130507-59-4P 130507-69-6P
167317-62-6P 167317-63-7P 167317-64-8P
167317-73-9P 167317-79-5P 167317-83-1P
167317-84-2P 167317-85-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(immunosuppressive structure-activity relationships of Brequinar and related cinchoninic acid derivs.)

L14 ANSWER 22 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 120:182596 CA

TITLE: The antilymphocytic activity of brequinar sodium and its potentiation by cytidine. Effects on lymphocyte proliferation and cytokine production

AUTHOR(S): Woo, Jacky; Lemster, Bonnie; Tamura, Kouichi; Starzl, Thomas E.; Thomson, Angus W.

CORPORATE SOURCE: Health Sci. Cent., Univ. Pittsburgh, Pittsburgh, PA, 15213, USA

SOURCE: Transplantation (1993), 56(2), 374-81
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English

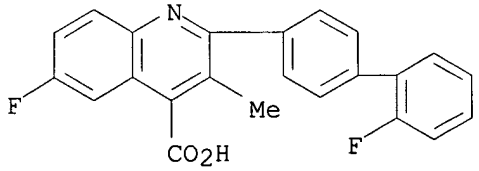
AB Based on its capacity to inhibit de novo pyrimidine biosynthesis by blocking **dihydroorotate** dehydrogenase activity, the antitumor

agent brequinar sodium (BQR) has emerged as a new immunosuppressive agent. Since BQR is known to prevent the synthesis of nucleotides during cell proliferation, the authors hypothesized that it would be highly effective in controlling strong lymphocyte proliferative responses but might be less effective in controlling comparatively weak responses that do not necessarily involve new nucleotide synthesis. The authors addressed this question by culturing murine spleen cells with different types of stimuli, including Con A, phorbol myristate acetate .+-. ionomycin, anti-CD3, and anti-Igs. Addn. of BQR (0.001 .mu.g/mL to 10 .mu.g/mL) at the start of a 72-h culture period caused dose-dependent inhibition of strong proliferative responses, induced either by Con A (5 .mu.g/mL) or PMA + ionomycin. A residual degree of proliferation persisted, however, even at the highest BQR concns. In contrast, no impairment of low-concn. Con A (0.5 or 0.1 .mu.g/mL), anti-CD3, or anti-Igs responses was obsd. In order to ascertain its role in arresting nucleotide synthesis, the authors attempted to reverse the inhibitory effect of BQR by adding exogenous uridine or cytidine to lymphocyte cultures. BQR's inhibitory activity was reversed completely by adding uridine at 0.1 mM. In contrast, combination of BQR and cytidine (0.1 mM) potentiated BQR's activity and abrogated anti-CD3 or anti-Igs-induced lymphocyte proliferation in a dose-dependent manner. A synergistic inhibitory action between BQR and cytidine was obsd. when the BQR concn. was higher than 0.1 .mu.g/mL and with cytidine at 0.1 mM. Prodn. of interleukin-2 and IL-4 was only slightly affected by BQR, but was significantly suppressed by coadministration of BQR and cytidine. Neither BQR (5 .mu.g/mL) on its own, however, nor combination of BQR with cytidine affected prodn. of mRNA for IL-2, IL-4, or interferon-.gamma., as detd. by reverse-transcription polymerase chain reaction. The authors' observations suggest that BQR may not only affect **dihydroorotate** dehydrogenase activity, but may also inhibit the enzyme cytidine deaminase, which converts cytidine to uridine. These antimetabolic effects of BQR complement the well-known cytokine synthesis inhibitory actions of FK506 or CsA. The combination of BQR and cytidine, however, offers a further possibility for inhibition of both cytokine prodn. and T and B cell proliferation, and may have potential for the control of graft rejection.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(lymphocyte proliferation and cytokine prodn. inhibition by, cytidine potentiation of, immunosuppression in relation to)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

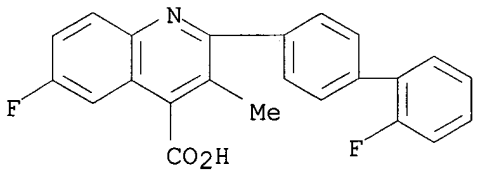
IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(lymphocyte proliferation and cytokine prodn. inhibition by, cytidine potentiation of, immunosuppression in relation to)

L14 ANSWER 23 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 120:245 CA
TITLE: Brequinar sodium: inhibition of dihydroorotic acid dehydrogenase, depletion of pyrimidine pools, and consequent inhibition of immune functions in vitro
AUTHOR(S): Simon, P.; Townsend, R. M.; Harris, R. R.; Jones, E. A.; Jaffee, B. D.
CORPORATE SOURCE: Div. Inflammatory Dis. Res., Du Pont Merck Pharm. Co., Wilmington, DE, USA
SOURCE: Transplantation Proceedings (1993), 25(3, Suppl. 2), 77-80
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Brequinar sodium [BQR; DuP 785, NSC 368390, 6-fluoro-2-(2'-fluoro-1-'-biphenyl-4-yl)3-methyl-4-quinoline carboxylic acid sodium salt] is a new agent recently found to have potent immunosuppressive activity. BQR is now in early clin. trials for kidney, liver, and heart transplantation. BQR causes a blockade of the de novo pyrimidine biosynthetic pathway through its effect on **dihydroorotate** dehydrogenase (DHODH). While agents that interfere with purine nucleotide biosynthesis have been used for both cancer and immunosuppression, inhibition of pyrimidine biosynthesis is a new target for obtaining immunosuppression. In this study, the authors examd. the effects of BQR on various in vitro immunoassays, the kinetics of the interaction of BQR with its target enzyme, DHODH, and the effect of BQR on the cellular nucleotide pools.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(dihydroorotic acid dehydrogenase inhibition and pyrimidine pools depletion, as immunosuppressant)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(dihydroorotic acid dehydrogenase inhibition and pyrimidine pools depletion, as immunosuppressant)

L14 ANSWER 24 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 119:131129 CA
TITLE: Effect of brequinar sodium on in vivo antibody production
AUTHOR(S): Yasunaga, C.; Cramer, D. V.; Cosenza, C. A.; Tuso, P. J.; Chapman, F. A.; Barnett, M.; Wu, G. D.; Putnam, B. A.; Makowka, L.
CORPORATE SOURCE: Cedars-Sinai Res. Inst., Cedars-Sinai Med. Cent., Los Angeles, CA, USA

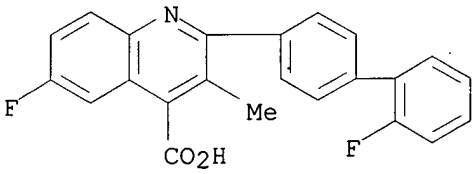
SOURCE: Transplantation Proceedings (1993), 25(3, Suppl. 2), 40-4
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Brequinar sodium (BQR) is a novel immunosuppressive agent that interferes with de novo pyrimidine synthesis through the selective inhibition of **dihydroorotate** dehydrogenase. This agent is highly effective in suppressing both the B- and T-cell-mediated immune responses. BQR is particularly effective as a single agent in preventing xenograft rejection, primarily due to the suppression of IgM antibody prodn. following placement of the graft. In a recent series of expts., the authors have examd. more closely the relationship between BQR treatment, antibody prodn., and the rejection of hamster-to-rat xenografts or cardiac allografts in sensitized individuals. The authors' results demonstrate that BQR is highly effective in preventing accelerated graft rejection of ACI heart grafts transplanted to presensitized LEW recipients and hamster-to-rat cardiac xenografts. In both cases, the prolongation of graft survival is assocd. with suppression of recipient antidonor antibody prodn.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(antibody formation response to)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(antibody formation response to)

L14 ANSWER 25 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 117:83050 CA

TITLE: Inhibition of **dihydroorotate** dehydrogenase activity by brequinar sodium

AUTHOR(S): Chen, Shih Fong; Perrella, Frank W.; Behrens, Davette L.; Papp, Lisa M.

CORPORATE SOURCE: Glenolden Lab., Du Pont Merck Pharm. Co., Glenolden, PA, 19036, USA

SOURCE: Cancer Research (1992), 52(13), 3521-7
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

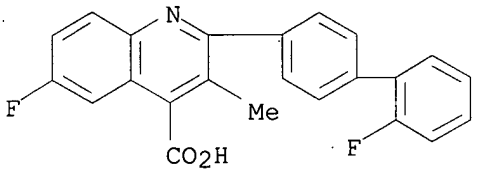
AB The novel anticancer drug candidate brequinar sodium (DuP 785, NSC 368390, 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid sodium salt) was shown previously to be an inhibitor of **dihydroorotate** dehydrogenase, the fourth enzyme of the de novo pyrimidine biosynthetic pathway. Brequinar sodium inhibits the activity

of this enzyme isolated from mammalian sources only but not those forms isolated from yeast or bacteria, which also use ubiquinone as the cofactor. Brequinar sodium also does not inhibit the activity of a sol. Zymobacterium oroticum **dihydroorotate** dehydrogenase which uses NAD+ as a cofactor. Brequinar sodium inhibits L1210 **dihydroorotate** dehydrogenase with mixed inhibition kinetics with respect to either the substrate (**dihydroorotate**) or the cofactor (ubiquinone Q6) with Ki' values in the 5-8 nM range. These results suggest that brequinar sodium inhibits **dihydroorotate** dehydrogenase by binding to the enzyme at a unique site that is distinct from the **dihydroorotate** or the ubiquinone-binding site. This binding site appears to be unique to the mammalian enzyme, because brequinar sodium does not inhibit the yeast, Escherichia coli, or Z. oroticum forms of the enzyme.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(**dihydroorotate** dehydrogenase of humans and lab. animals inhibition by, neoplasm-inhibiting activity in relation to)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(**dihydroorotate** dehydrogenase of humans and lab. animals inhibition by, neoplasm-inhibiting activity in relation to)

L14 ANSWER 26 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 117:39989 CA

TITLE: The "anti-pyrimidine effect" of hypoxia and brequinar sodium (NSC 368390) is of consequence for tumor cell growth

AUTHOR(S): Loeffler, Monika

CORPORATE SOURCE: Sch. Med., Philipps-Univ., Marburg, 3550, Germany

SOURCE: Biochemical Pharmacology (1992), 43(10), 2281-7
CODEN: BCPCA6; ISSN: 0006-2952

DOCUMENT TYPE: Journal

LANGUAGE: English

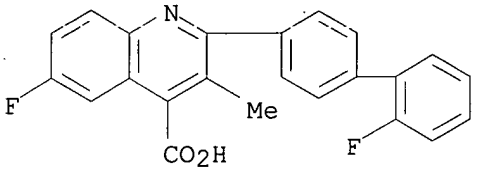
AB The rationale of the present study was to investigate the simultaneous effect of hypoxia and drugs with an "anti-pyrimidine effect" on tumor cell proliferation to evaluate putative changes in the sensitivity of cells to these kinds of chemotherapeutic treatment on reduced O2 tension. Pyrimidine de novo biosynthesis, at the stage of respiratory chain-dependent **dihydroorotate** dehydrogenase, was found to be a biochem. target site for oxygen deficiency as well as for brequinar sodium (6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid sodium salt) (brequinar). Increasing drug concns. (0.1-50 .mu.M) reduced the proliferation rate of in vitro cultured Ehrlich ascites tumor cells (IC50 = 0.25 .mu.M). Decreasing concns. of O2 reduced the proliferation rate (50% at .apprx.3.5% O2). Brequinar at 2.5 and 12.5 .mu.M stimulated the incorporation of exogenous [14C]uridine into RNA to 140 and 190% of controls, resp., as a result of active salvage pathways,

whereas it decreased the incorporation of [14C]NaHCO3 by the de novo pathway (to 20 and 5% of controls, resp.). Cells routinely grown in glucose-free, uridine-supplemented medium were resistant to 12.5 .mu.M of the drug. The complete growth pattern of the tumor cells (increase in cell no. and protein, RNA and DNA content of cultures during a 24-h culture period) was examd. (i) on reducing the O2 tension of the atm. stepwise from 20 to 1% O2; (ii) on addn. of 0.125 .mu.M brequinar; and (iii) under both conditions. The combination was found to give an additive inhibitory effect under moderate hypoxia (5-20% O2) and a greater than additive effect if the oxygen tension was further reduced (1-5%).

IT **96201-88-6**, NSC 368390
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of, as pyrimidine antimetabolite, hypoxia enhancement of)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, NSC 368390
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of, as pyrimidine antimetabolite, hypoxia enhancement of)

L14 ANSWER 27 OF 38 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 116:207444 CA

TITLE: Differential susceptibility of **dihydroorotate** dehydrogenase/oxidase to brequinar sodium (NSC 368 390) in vitro

AUTHOR(S): Lakaschus, Gunda; Loeffler, Monika

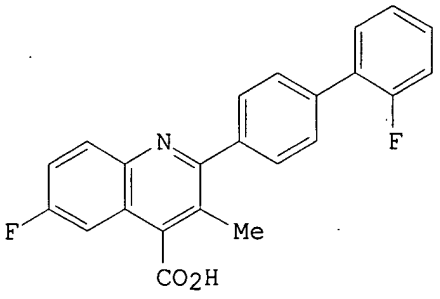
CORPORATE SOURCE: Sch. Med., Philipps-Univ. Marburg, Marburg, 3550, Germany

SOURCE: Biochemical Pharmacology (1992), 43(5), 1025-30
CODEN: BCPCA6; ISSN: 0006-2952

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



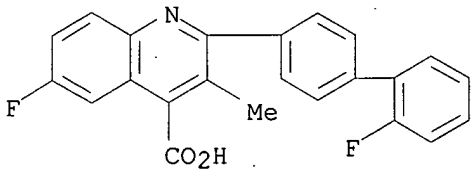
I

AB To verify the assumption of a specific and potent drug action on de novo pyrimidine biosynthesis, isolated **dihydroorotate** dehydrogenase (DHO-DH)(EC 1.3.3.1) was exposed to Brequinar SodiumTM (I sodium) (NSC 368 390). The membrane-bound DHO-DH was purified to apparent homogeneity (25,000-fold) from rat liver mitochondria in six steps via detergent extn. and subsequent chromatog. using the dye ligand MatrexTM Gel Orange A. Using mol. mechanistic studies (MM2) this ligand was found to mimic closely the stereochem. conformation of I SDS-PAGE revealed two protein bands for the purified enzyme with apparent mol. masses of 58 (major) and 68 kDa (minor). In vitro, two modes of action of the DHO-DH are possible: (i) acting as a dehydrogenase in the presence of ubiquinone as proximal electron acceptor and (ii) direct reaction with oxygen as oxidase. A novel assay for the measurement of the oxidase activity was adapted using leucodichlorofluorescein-diacetate. Inhibition expts. revealed a striking difference in the susceptibility of DHO-dehydrogenase/oxidase to I:apparent Ki = 6.09 nM (DHO; ubiquinone, but Ki = 3.10 mM (DHO; O2). Anal. of initial velocity expts. showed non-competitive inhibition of I with respect to the substrate dihydroorotic acid in both assays (dehydrogenase and oxidase). The inhibitory effect of the latter was compared to that of the competitive inhibitor 5-aza-**dihydroorotate** (apparent Ki = 15 .mu.M). The present kinetic data on the action of the purified rodent DHO-DH with I and computer-aided analyses provide a better insight into the drug-enzyme interaction.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(**dihydroorotate** dehydrogenase/oxidase susceptibility to, as antitumor agent, mol. mechanics in)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(**dihydroorotate** dehydrogenase/oxidase susceptibility to, as antitumor agent, mol. mechanics in)

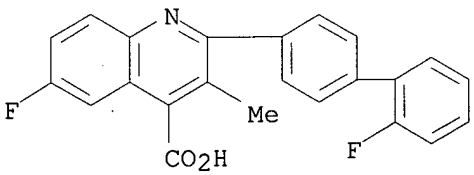
L14 ANSWER 28 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 116:187641 CA

TITLE: Brequinar potentiates 5-fluorouracil antitumor activity in a murine model colon 38 tumor by tissue-specific modulation of uridine nucleotide pools
AUTHOR(S): Pizzorno, Giuseppe; Wiegand, Rosemary A.; Lentz, Sarah K.; Handschumacher, Robert E.
CORPORATE SOURCE: Sch. Med., Yale Univ., New Haven, CT, 06510, USA
SOURCE: Cancer Research (1992), 52(7), 1660-5
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Modulation of pyrimidine metab. or the metabolic fate of 5-fluorouracil by a no. of different agents has permitted a significant increase in the response rate to this agent, particularly for colorectal cancers. Brequinar, a noncompetitive inhibitor of mitochondrial **dihydroorotate** dehydrogenase has been shown to achieve a tumor-specific modulation of the therapeutic effect of 5-fluorouracil. A selective decrease of uridine nucleotide pools in Colon tumor 38 compared to normal tissues of C57/BL6 mice was obsd. after Brequinar administration. This effect was achieved with very low nontherapeutic doses of Brequinar (8 to 27% of the max. tolerated dose in this model). Pretreatment with Brequinar 4 and 24 h prior to administration of [3H]fluorouracil significantly increased incorporation of the fluoropyrimidine into Colon 38 tumor RNA, while minimal effects were seen in normal tissues of C57/BL6 mice. Brequinar (15, 30, and 50 mg/kg) was administered 4 h prior to fluorouracil (85 mg/kg) on a weekly basis in Colon 38-bearing mice. All combinations potentiated 5-fluorouracil antitumor activity and the lowest dose of Brequinar (15 mg/kg) showed a reduced toxicity (wt. loss) compared to the same dose of 5-fluorouracil as a single agent. When Brequinar preceded fluorouracil by 24 h, greater toxicity and less antitumor activity were obsd. A comparison of the optimal Brequinar-fluorouracil regimen with a previously optimized N-(phoshonoacetyl-L-aspartic acid-fluorouracil combination in Colon 38 tumor indicated that Brequinar-fluorouracil was more effective and less toxic.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(fluorouracil antitumor activity potentiation by, uridine nucleotide pool depletion in)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(fluorouracil antitumor activity potentiation by, uridine nucleotide pool depletion in)

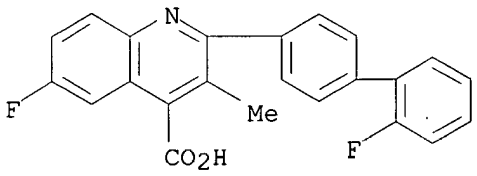
L14 ANSWER 29 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 116:187635 CA
TITLE: In vitro and in vivo studies on the combination of Brequinar sodium (DUP-785; NSC 368390) with 5-fluorouracil; effects of uridine

AUTHOR(S): Peters, G. J.; Kraal, I.; Pinedo, H. M.
CORPORATE SOURCE: Dep. Oncol., Free Univ. Hosp., Amsterdam, 1007 MB, Neth.
SOURCE: British Journal of Cancer (1992), 65(2), 229-33
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Brequinar sodium is a potent inhibitor of the pyrimidine de novo formation enzyme **dihydroorotate** dehydrogenase, leading to a depletion of pyrimidine nucleotides, which could be reversed by uridine. In vitro studies were done to investigate the effect of different physiol. concns. of uridine on the inhibition of the growth of colon tumor cells by Brequinar and the effect of the nucleoside transport inhibitor dipyridamole or the combination of Brequinar with 5-fluorouracil (5FU). Uridine at 1 .mu.M slightly reversed the growth inhibition by Brequinar, while the effect of 5-500 .mu.M uridine was greater. At Brequinar concns. >30 .mu.M, uridine could not reverse the growth-inhibitor effects. Addn. of dipyridamole could only partially prevent the reversing effects of uridine. The combination of Brequinar and 5FU was more than additive in the absence of uridine in the culture medium, but not in the presence of uridine. The combination of Brequinar and 5FU was tested in vivo in 2 murine colon tumor models, Colon 26 and Colon 38. The dose schedule of both compds. was very important. In Colon 38 no potentiating effect of Brequinar on the action of 5FU could be obsd. In Colon 26 a more than additive effect could be obsd. Since uridine concns. are considerably different in these tumors (higher in Colon 38), uridine concn. is an important determinant in the effects of combinations of Brequinar and 5FU.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(colon neoplasm inhibitor by fluorouracil and, uridine and dipyridamole effect on)

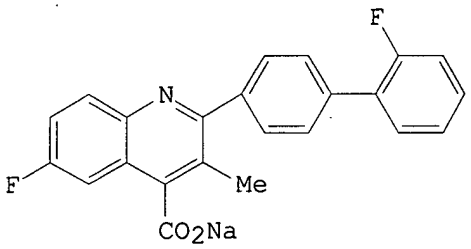
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(colon neoplasm inhibitor by fluorouracil and, uridine and dipyridamole effect on)

L14 ANSWER 30 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 115:174224 CA
TITLE: Cellular pharmacology of DUP-785, a new anticancer agent
AUTHOR(S): Anderson, Lawrence W.; Strong, John M.; Cysyk, Richard L.
CORPORATE SOURCE: Lab. Biol. Chem., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Cancer Communications (1989), 1(6), 381-7
CODEN: CNCMET; ISSN: 0955-3541
DOCUMENT TYPE: Journal
LANGUAGE: English

GI



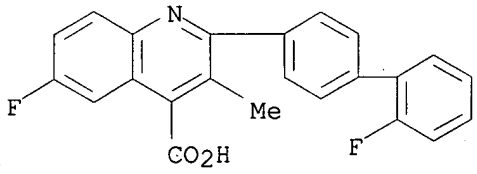
I

AB DUP-785 (I), a new inhibitor of **dihydroorotate** dehydrogenase, is currently undergoing clin. evaluation for anticancer activity. A gas chromatog.-mass spectroscopy method was developed method to quantitate dehydroorotate that accumulates in cultures of L1210 cells exposed to growth inhibitory concns. of DUP-785. This method was used to follow the onset, extent, and duration of inhibition of de novo pyrimidine synthesis in intact L1210 cells and to compare this inhibition with cell proliferation and cellular concns. of pyrimidine nucleotides. There were direct relations between inhibition of de novo pyrimidine synthesis, changes in pyrimidine nucleotide concns., and cell proliferation following short (<24 h) drug exposures; with prolonged exposures (>24 h); however, there was a departure from these relationships in that restoration of pyrimidine nucleotide pools and de novo pyrimidine pathway activity did not restore cell proliferation. Exposure of L1210 cells to 15 .mu.M DUP-785 produced a max. cell kill (99.9% as detd. by cloning efficiency) at 24 h, and no increase in cell kill was obsd. with drug exposure up to 96 h.

IT **96201-88-6**, DUP-785
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as neoplasm inhibitor, mechanism of, pyrimidine formation in)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

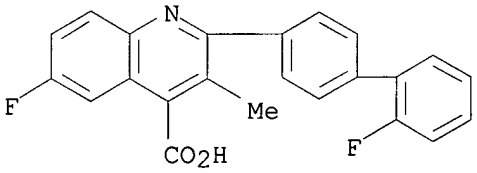
IT **96201-88-6**, DUP-785
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as neoplasm inhibitor, mechanism of, pyrimidine formation in)

L14 ANSWER 31 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 114:177903 CA
TITLE: Effects of brequinar and ciprofloxacin on de novo nucleotide biosynthesis in mouse L1210 leukemia
AUTHOR(S): Lyons, Stephen D.; Christopherson, Richard I.
CORPORATE SOURCE: Dep. Biochem., Univ. Sydney, Sydney, 2006, Australia
SOURCE: Biochemistry International (1990), 22(6), 939-49
CODEN: BIINDF; ISSN: 0158-5231
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The exposure of mouse L1210 leukemia cells to 25 .mu.M brequinar for 4 h resulted in large accumulations of N-carbamyl-L-aspartate and L-**dihydroorotate** to cellular concns. of 8.5 mM and 0.8 mM, resp., while UTP and CTP decreased to 4% of their initial levels; incorporation of [14C]bicarbonate into nucleic acids (DNA and RNA) decreased to 47%. The data provide direct evidence for the inhibition of **dihydroorotate** dehydrogenase by brequinar in growing cells. Exposure of leukemia cells to 200 .mu.M ciprofloxacin for 4 h did not affect the de novo pyrimidine nucleotide biosynthesis or the incorporation of [14C]bicarbonate into nucleic acids but resulted in a general decrease in nucleoside triphosphates, with concomitant accumulation of nucleoside mono- and diphosphates (the adenylate energy charge decreased from 0.89 to 0.69), consistent with the inhibition of electron transport chain or the uncoupling of oxidative phosphorylation.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(**dihydroorotate** dehydrogenase in leukemia cells inhibition by, nucleotide formation in relation to)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(**dihydroorotate** dehydrogenase in leukemia cells inhibition by, nucleotide formation in relation to)

L14 ANSWER 32 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 114:35413 CA
TITLE: Structure-activity relationship of quinoline carboxylic acids. A new class of inhibitors of **dihydroorotate** dehydrogenase
AUTHOR(S): Chen, Shih Fong; Papp, Lisa M.; Ardecky, Robert J.; Rao, Ganti V.; Hesson, David P.; Forbes, Martin; Dexter, Daniel L.
CORPORATE SOURCE: Pharm. Biotechnol. Res. Dev. Div., E. I. Du Pont de Nemours and Co., Wilmington, DE, 19898, USA
SOURCE: Biochemical Pharmacology (1990), 40(4), 709-14
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

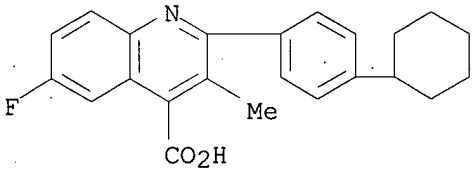
GI For diagram(s), see printed CA Issue.

AB The novel anticancer drug candidate brequinar sodium [DuP 785, I] and other quinoline carboxylic acids inhibit **dihydroorotate** dehydrogenase, the fourth enzyme in the de novo pyrimidine biosynthetic pathway leading to the formation of UMP. Sixty-nine quinoline 4-carboxylic acid analogs were analyzed as inhibitors of L1210 **dihydroorotate** dehydrogenase. This structure-activity relationship study identified three crit. regions of brequinar sodium and its analogs, where specific substitutions are required for the inhibition of the activity of **dihydroorotate** dehydrogenase. The three principal regions are (i) the C(2) position where bulky hydrophobic substituents are necessary, (ii) the C(4) position which has a strict requirement for the carboxylic acid and its corresponding salts, and (iii) the benzo portion of the quinoline ring with appropriate substitutions. These results will be useful in the elucidation of the precise nature of the interaction between brequinar sodium and **dihydroorotate** dehydrogenase.

IT **96187-26-7**
RL: BIOL (Biological study)
(**dihydroorotate** dehydrogenase inhibition by, antitumor activity of, structure in relation to)

RN 96187-26-7 CA

CN 4-Quinolinecarboxylic acid, 2-(4-cyclohexylphenyl)-6-fluoro-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-26-7 96187-27-8 96187-30-3**
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96187-64-3 96187-73-4 96201-24-0
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96201-52-4 96201-54-6 96201-88-6
96202-45-8 96202-55-0 130507-32-3
130507-33-4 130507-51-6 130507-53-8
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130507-61-8 130507-62-9 130507-63-0
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130507-67-4 130507-68-5 130507-69-6
RL: BIOL (Biological study)
(**dihydroorotate** dehydrogenase inhibition by, antitumor activity of, structure in relation to)

L14 ANSWER 33 OF 38 CA COPYRIGHT 2003 ACS on STN

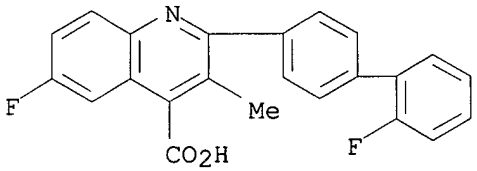
ACCESSION NUMBER: 113:34450 CA

TITLE: The relation between inhibition of cell growth and of dihydroorotic acid dehydrogenase by Brequinar sodium [Erratum to document cited in CA111(13):108613b]

AUTHOR(S): De Kant, E.; Pinedo, H. M.; Laurensse, E.; Peters, G. J.

CORPORATE SOURCE: Dep. Oncol., Free Univ. Hosp., Amsterdam, 1007 MB, Neth.

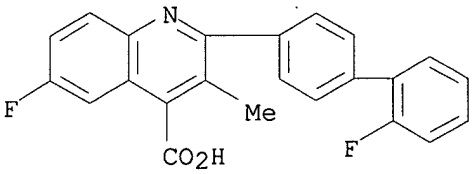
SOURCE: Cancer Letters (Shannon, Ireland) (1989), 47(3), 229
CODEN: CALEDQ; ISSN: 0304-3835
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An error in the text has been cor. The error was not reflected in the abstr. or the index entries.
IT **96201-88-6**
RL: PRP (Properties)
(cytotoxicity of, to tumor cells of humans and lab. animals, dihydroorotic acid dehydrogenase inhibition in relation to (Erratum))
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

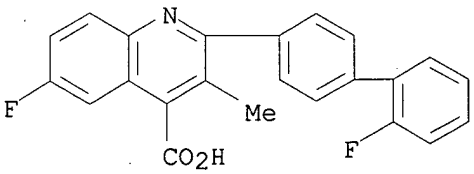
IT **96201-88-6**
RL: PRP (Properties)
(cytotoxicity of, to tumor cells of humans and lab. animals, dihydroorotic acid dehydrogenase inhibition in relation to (Erratum))

L14 ANSWER 34 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 112:191525 CA
TITLE: The relationship between dihydroorotic acid dehydrogenase and in vitro and in vivo cytostatic effects of brequinar sodium (DUP-785; NSC 368390)
AUTHOR(S): Peters, Godefridus J.; Laurensse, Emile; Kant, Erik De; Nadal, Jorge C.; Pinedo, Herbert M.
CORPORATE SOURCE: Dep. Oncol., Free Univ. Hosp., Amsterdam, 1007 MB, Neth.
SOURCE: Advances in Experimental Medicine and Biology (1989), 253B(Purine Pyrimidine Metab. Man 6, Pt. B), 375-82
CODEN: AEMBAP; ISSN: 0065-2598
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To better understand the role of dihydroorotic acid dehydrogenase (DHODH) in the synthesis of pyrimidine nucleotides and in the antitumor action of brequinar sodium (BS), the activity of DHODH and the inhibition by BS was investigated in several cell lines. The cell sensitivity to BS was related to the extent of DHODH inhibition in vitro. In vivo retention of DHODH inhibition parallelled the effects on uridine phosphate.
IT **96187-53-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dihydroorotic acid inhibition in relation to antitumor activity of)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dihydroorotic acid inhibition in relation to antitumor activity of)

L14 ANSWER 35 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 111:108613 CA
TITLE: The relation between inhibition of cell growth and of dihydroorotic acid dehydrogenase by Brequinar Sodium
AUTHOR(S): De Kant, E.; Pinedo, H. M.; Laurensse, E.; Peters, G. J.
CORPORATE SOURCE: Dep. Oncol., Free Univ. Hosp., Amsterdam, 1007 MB, Neth.
SOURCE: Cancer Letters (Shannon, Ireland) (1989), 46(2), 123-7
CODEN: CALEDQ; ISSN: 0304-3835
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The growth inhibitory effects of Breqinar Sodium (DUP-785; NSC 368390) in 7 different cell lines were related to growth rates and to the inhibition of dihydroorotic acid dehydrogenase (DHO-DH) activity. IC50 values were 0.2-5.8 .mu.M; the fastest growing cell line was least sensitive. Despite a large variation in sensitivity, basal activity of DHO-DH showed little variation (only 2-fold) between the different cell lines. Residual activity of DHO-DH in the presence of Brequinar Sodium varied 30-fold. Drug sensitivity correlated with this residual DHO-DH activity; DHO-DH activity was only slightly inhibited by Breqinar Sodium in the most resistant lines, and almost completely in the most sensitive lines.
IT **96201-88-6**, NSC 368390
RL: PRP (Properties)
(cytotoxicity of, to tumor cells of humans and lab. animals, dihydroorotic acid dehydrogenase inhibition in relation to)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, NSC 368390
RL: PRP (Properties)
(cytotoxicity of, to tumor cells of humans and lab. animals, dihydroorotic acid dehydrogenase inhibition in relation to)

L14 ANSWER 36 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 109:163037 CA
TITLE: DUP 785 (NSC 368390): schedule-dependency of growth-inhibitory and antipyrimidine effects
AUTHOR(S): Schwartsmann, G.; Peters, G. J.; Laurensse, E.; De Waal, F. C.; Loonen, A. H.; Leyva, A.; Pinedo, H. M.
CORPORATE SOURCE: Dep. Oncol., Free Univ. Hosp., Amsterdam, Neth.
SOURCE: Biochemical Pharmacology (1988), 37(17), 3257-66
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
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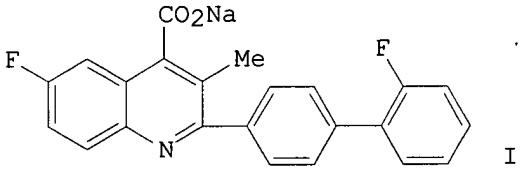
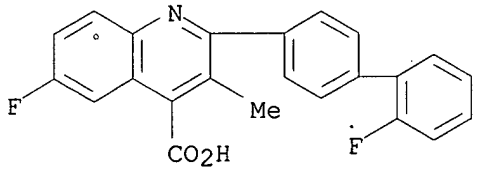


I

AB DUP 785 (I) is a new inhibitor of pyrimidine de novo biosynthesis with antitumor activity against several exptl. tumors. DUP 785 inhibits the mitochondrial enzyme **dihydroorotate** dehydrogenase, blocking the conversion of **dihydroorotate** to orotate. The influence of exposure time to DUP 785 on its growth-inhibitory effects was examd. in L1210 murine leukemia and WiDR human adenocarcinoma cells and the effects of pyrimidine (deoxy)nucleosides on reversal of growth-inhibition was also detd. The results indicate that UMP depletion is crit. for the growth-inhibitory effects of DUP 785 in vitro. Prolonged exposure of cells to DUP785 seems necessary for a long-lasting depletion of intracellular pyrimidine nucleotide pools. This leads to a block in RNA and DNA synthesis and to the accumulation of cells in the S-phase of the cell cycle, causing growth-inhibition. These findings suggest a need for prolonged drug exposure in clin. trials of DUP 785.

IT **96201-88-6**, NSC 368390
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibition by, schedule dependency of, pyrimidine nucleotide depletion in)

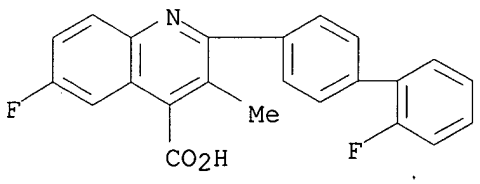
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



Na

IT **96201-88-6**, NSC 368390
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibition by, schedule dependency of, pyrimidine nucleotide depletion in)

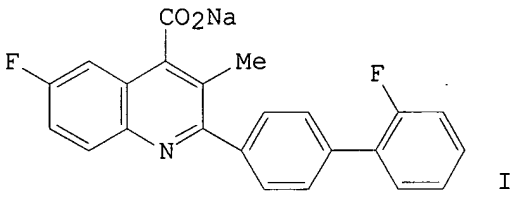
L14 ANSWER 37 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 108:289 CA
TITLE: Inhibition of pyrimidine de novo synthesis by DUP-785 (NSC 368390)
AUTHOR(S): Peters, G. J.; Sharma, S. L.; Laurensse, E.; Pinedo, H. M.
CORPORATE SOURCE: Dep. Oncol., Free Univ. Hosp., Amsterdam, 1007 MB, Neth.
SOURCE: Investigational New Drugs (1987), 5(3), 235-44
CODEN: INNDDK; ISSN: 0167-6997
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The concn. of DUP 785 causing 50% growth inhibition in L1210 leukemia cells and M5 melanoma cells after 48 h of culture were 5.8 and 0.6 .mu.M, resp. DUP-785 had to be present continuously in the culture. Growth inhibition by 25 .mu.M DUP-785 could be prevented by addn. of 1 mM uridine or orotic acid to cultures of these cell lines; in M5 cells, cytidine was also able to prevent growth inhibition. Dihydroorotic acid (DHO) and carbamylaspartate were not able to prevent growth inhibition by DUP-785. The accumulation of orotic acid and of orotidine induced by incubation with 1 .mu.M pyrazofurin, an inhibitor of the orotate phosphoribosyltransferase-orotidinemonophosphate decarboxylase complex, was prevented by addn. of DUP-785 to the culture medium. The effect of DUP-785 on DHO dehydrogenase (DHO-DH) was measured. DHO-DH was assayed in isolated rat liver mitochondria. The Km for L-DHO was .apprx.12 .mu.M. DUP-785 appeared to be a potent inhibitor of DHO-DH, with an apparent Ki of .apprx.0.1 .mu.M and an apparent Ki' of .apprx.0.8 .mu.M. The mode of inhibition appeared to be a linear mixed type. After exposure of L1210 cells to 25 .mu.M DUP-785 for 2 h, DHO-DH was almost completely inhibited. After suspension in fresh medium without drug, DHO-DH activity recovered to .apprx.60% after 24 h. In conclusion, DUP-785 is a potent inhibitor of pyrimidine de novo biosynthesis, by inhibition of the mitochondrial enzyme DHO-DH.
IT **96201-88-6**, NSC 368390
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibition by, pyrimidine formation inhibition in)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



Na

IT **96201-88-6**, NSC 368390
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibition by, pyrimidine formation inhibition in)

L14 ANSWER 38 OF 38 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 105:202816 CA
TITLE: Mechanism of action of the novel anticancer agent 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid sodium salt (NSC 368390): inhibition of de Novo pyrimidine nucleotide biosynthesis
AUTHOR(S): Chen, Shih Fong; Ruben, Regina L.; Dexter, Daniel L.
CORPORATE SOURCE: Biomed. Prod. Dep., E.I. Du Pont de Nemours and Co., Inc., Wilmington, DE, 19898, USA
SOURCE: Cancer Research (1986), 46(10), 5014-19
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

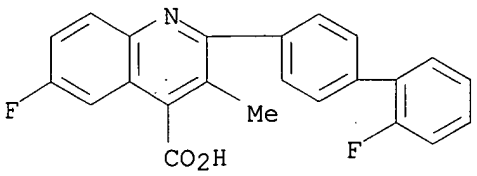
AB Exposure of cultured clone A human colon tumor cells to 25-75 .mu.M of NSC 368390 [6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid sodium salt, DuP 785] (I) [**96201-88-6**] for 48-72 h resulted in a 99.9% cell kill as detd. by clonogenic assay. Cells exposed to NSC 368390 became depleted in intracellular pools of UTP [63-39-8] and CTP [65-47-4]. Both UTP and CTP were decreased to 50% of levels in control cells at 3 h and were undetectable at 15 h after addn. of 25 .mu.M of NSC 368390 to the cultures. Similar effects were obsd. in L1210 leukemia cells. Addn. of 0.1 mM of uridine [58-96-8] or cytidine [65-46-3] restored intracellular pools of UTP and CTP to control levels and rescued clone A cells from NSC 368390 cytotoxicity. Addn. of uridine circumvented NSC 368390 cytotoxicity in L1210 cells, but addn. of cytidine did not. This result is consistent with the fact that L1210 cells lack cytidine deaminase and thus cannot form uridine or its anabolites from cytidine. Thus, NSC 368390 inhibits a step in the de novo biosynthetic pathway leading to UMP [58-97-9]. When NSC 368390 was tested for its effect on the enzymes that comprise the de novo pathway leading to the formation of UMP NSC 368390 was a potent inhibitor of **dihydroorotate** dehydrogenase [9029-03-2], the fourth enzyme in the pathway. This study demonstrated that NSC 368390 exerts its tumoricidal effect by inhibiting a step in de novo pyrimidine biosynthesis resulting in the depletion of crit. precursors for RNA and DNA synthesis.

IT **96201-88-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(neoplasm-inhibiting activity of, mechanism of, inhibition of de novo pyrimidine nucleotide formation in)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(neoplasm-inhibiting activity of, mechanism of, inhibition of de novo pyrimidine nucleotide formation in)

=> d ibib abs fhitstr hitrn 1-8

L17 ANSWER 1 OF 8 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 135:24657 CA

TITLE: Selective cellular targeting: multifunctional delivery vehicles

INVENTOR(S): Glazier, Arnold

PATENT ASSIGNEE(S): Drug Innovation + Design, Inc., USA

SOURCE: PCT Int. Appl., 981 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036003	A2	20010525	WO 2000-US31262	20001114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001016075	A5	20010530	AU 2001-16075	20001114
EP 1255567	A1	20021113	EP 2000-978631	20001114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003138432	A1	20030724	US 2000-738625	20001215

PRIORITY APPLN. INFO.: US 1999-165485P P 19991115
US 2000-239478P P 20001011

US 2000-241937P P 20001020
WO 2000-US31262 W 20001114
US 2000-712465 B1 20001115

AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

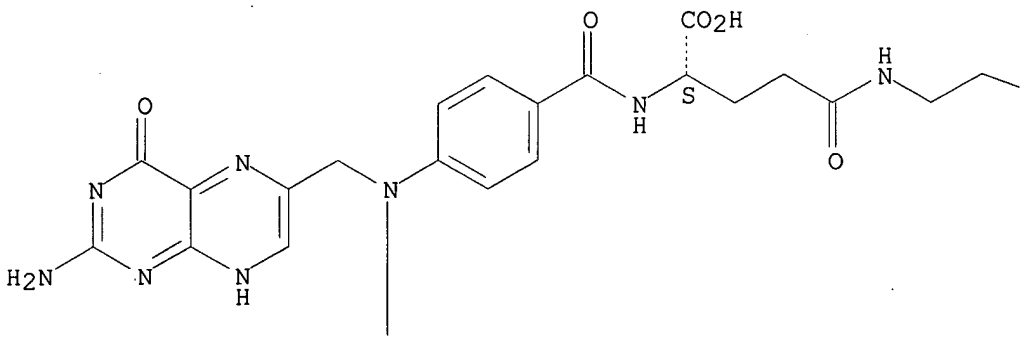
IT **341553-59-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

RN 341553-59-1 CA

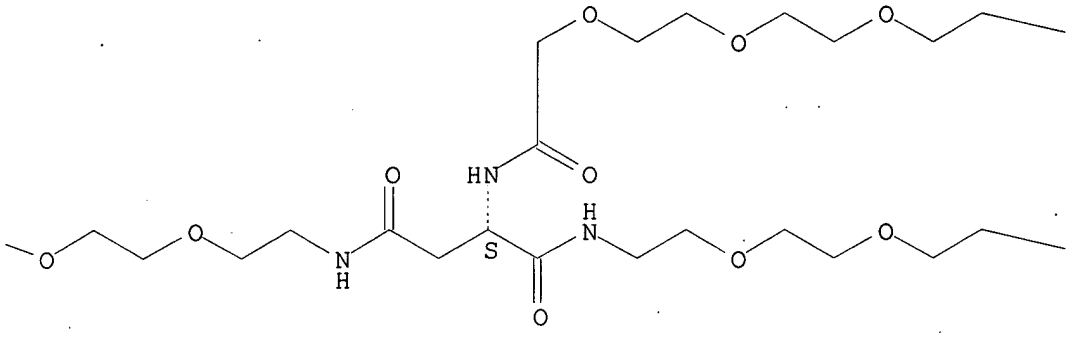
CN Quinolinium, 1-[[[7-[[(21S,38S)-21-[(16S)-18-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl][[[3-[[(3-carboxy-1-oxopropoxy)methoxy]carbonyl]-4-[(2-oxido-1,3,2-dioxaphosphorinan-2-yl)oxy]phenyl]methoxy]carbonyl]amino]phenyl]-16-carboxy-2,13,18-trioxo-6,9-dioxa-3,12,17-triazaoctadec-1-yl]-59,61-dicarboxy-38-(1,14-dioxo-5,8,11-trioxa-2,15-diazadocos-1-yl)-57-hydroxy-57-oxido-2,7,20,23,36,40,54-heptaoxo-10,13,16,25,28,31,34,44,47,50-decaoxa-3,6,19,22,37,41,53-heptaaza-57-phosphahenhexacont-1-yl]dithio]-8-[(carboxymethyl)dithio]-1,5-dihydro-3-oxido-2,4,3-benzodioxaphosphepin-3-yl]oxy]methyl]-4-carboxy-6-fluoro-2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methyl-, chloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

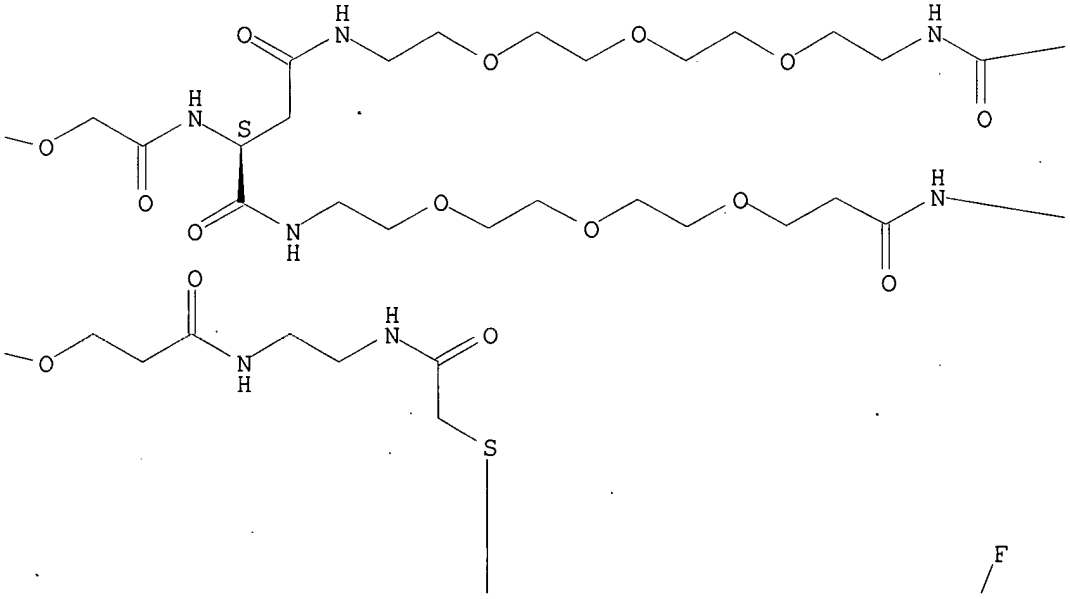
PAGE 1-A



PAGE 1-B



PAGE 1-C



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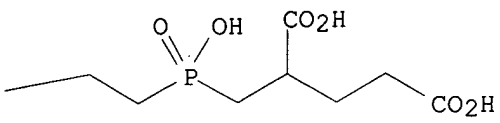
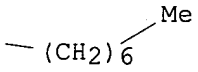
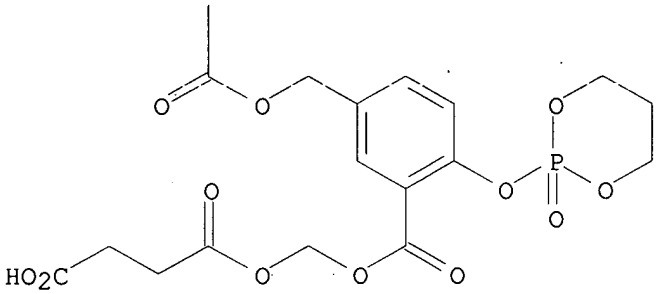
PAGE 1-D



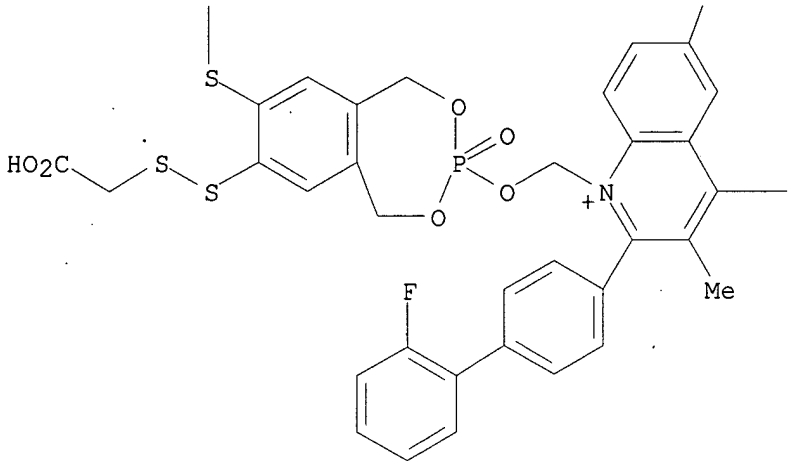


PAGE 2-A



● Cl^-

PAGE 2-C



PAGE 2-D

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IT **341553-59-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

IT **341553-60-4P 341553-61-5P**
RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

L17 ANSWER 2 OF 8 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 131:281604 CA
TITLE: Treatment of chemotherapeutic agent and antiviral agent toxicity with acylated pyrimidine nucleosides
INVENTOR(S): Von Borstel, Reid; Bamat, Michael K.
PATENT ASSIGNEE(S): Pro-Neuron, Inc., USA
SOURCE: U.S., 31 pp., Cont.-in-part U. S. Ser. 176,485.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

US 5968914	A	19991019	US 1995-472210	19950607
EP 712629	A1	19960522	EP 1995-203050	19881027
EP 712629	B1	20030618		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 10001436	A2	19980106	JP 1997-36734	19881027
JP 2001192335	A2	20010717	JP 2000-379524	19881027
CA 2111571	AA	19930121	CA 1992-2111571	19920605
ES 2160579	T3	20011116	ES 1992-914215	19920625
ZA 9204975	A	19930428	ZA 1992-4975	19920703
IN 175688	A	19950812	IN 1992-CA473	19920706
US 5246708	A	19930921	US 1992-911379	19920713
US 5470838	A	19951128	US 1992-997657	19921230
US 5583117	A	19961210	US 1993-140475	19931025
US 6020320	A	20000201	US 1993-153163	19931117
US 5736531	A	19980407	US 1993-176485	19931230
IN 177670	A	19970215	IN 1994-CA701	19940902
US 5770582	A	19980623	US 1995-419767	19950410
US 5691320	A	19971125	US 1995-465454	19950605
US 6054441	A	20000425	US 1995-463790	19950605
US 6060459	A	20000509	US 1995-465016	19950605
US 6258795	B1	20010710	US 1995-466145	19950606
US 6316426	B1	20011113	US 1995-466144	19950606
US 6232298	B1	20010515	US 1995-479519	19950607
US 6274563	B1	20010814	US 1995-479349	19950607
US 6348451	B1	20020219	US 1995-478736	19950607
CA 2223640	AA	19961219	CA 1996-2223640	19960606
WO 9640165	A1	19961219	WO 1996-US10067	19960606
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
AU 9661114	A1	19961230	AU 1996-61114	19960606
AU 724805	B2	20000928		
EP 831849	A1	19980401	EP 1996-918461	19960606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CN 1192149	A	19980902	CN 1996-195929	19960606
JP 10511689	T2	19981110	JP 1996-502184	19960606
JP 2003201240	A2	20030718	JP 2003-721	19960606
US 2001025032	A1	20010927	US 1999-249790	19990216
US 6344447	B2	20020205		
AU 9952624	A1	19991202	AU 1999-52624	19991001

PRIORITY APPLN. INFO.:

US 1987-115923	B2	19871028
US 1987-115929	B2	19871028
US 1989-438493	B2	19890627
US 1990-487984	B2	19900205
US 1991-724340	B2	19910705
US 1992-903107	B2	19920625
US 1993-61381	B2	19930514
US 1993-176485	A2	19931230
US 1988-186031	B2	19880425
EP 1988-910239	A3	19881027
JP 1988-509176	A3	19881027
JP 1994-303877	A3	19881027
US 1989-341925	B1	19890421
US 1990-533933	B1	19900605
US 1991-653882	B2	19910208

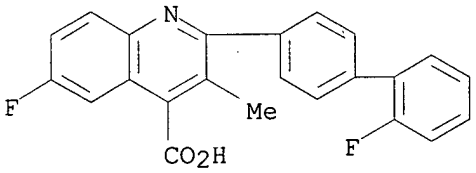
US	1991-737913	B3 19910729
IN	1992-CA473	A1 19920706
US	1992-911379	A3 19920713
US	1992-925931	B2 19920807
US	1992-958598	B3 19921007
US	1992-987730	B2 19921208
US	1992-997657	A3 19921230
US	1993-96407	B1 19930726
US	1993-98884	B1 19930729
US	1993-158799	B2 19931201
US	1994-266897	B3 19940701
US	1994-289214	A3 19940812
US	1995-472210	A 19950607
AU	1995-29150	A3 19950630
JP	1997-502184	A3 19960606
WO	1996-US10067	W 19960606

AB Compds., compns., and methods are disclosed for treatment and prevention of toxicity due to chemotherapeutic agents and antiviral agents. Disclosed are acylated derivs. of nonmethylated pyrimidine nucleosides. These compds. are capable of attenuating damage to the hematopoietic system in animals receiving antiviral or antineoplastic chemotherapy.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of chemotherapeutic agent and antiviral agent toxicity with acylated pyrimidine nucleosides)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of chemotherapeutic agent and antiviral agent toxicity with acylated pyrimidine nucleosides)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 8 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 131:29577 CA

TITLE: Anion exchange HPLC for obtaining L-dihydroorotic acid and use thereof

INVENTOR(S): Milbert, Ulrike; Bartlett, Robert; Ruuth, Eric; Fudali, Claude

PATENT ASSIGNEE(S): Hoechst Marion Roussel Deutschland GmbH, Germany

SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9930146	A1	19990617	WO 1998-EP7972	19981208
W: AU, BR, CA, CN, CZ, HU, ID, IN, JP, KR, MX, PL, RU, TR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 933633	A1	19990804	EP 1997-121848	19971211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2315326	AA	19990617	CA 1998-2315326	19981208
AU 9918775	A1	19990628	AU 1999-18775	19981208
AU 747993	B2	20020530		
EP 1036319	A1	20000920	EP 1998-963546	19981208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
BR 9813559	A	20001010	BR 1998-13559	19981208
JP 2001526387	T2	20011218	JP 2000-524655	19981208
US 6545006	B1	20030408	US 2000-581142	20001211

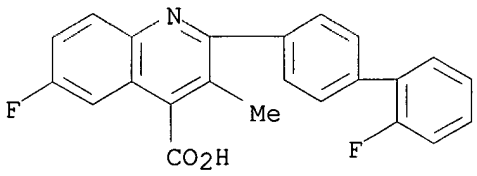
PRIORITY APPLN. INFO.: EP 1997-121848 A 19971211
WO 1998-EP7972 W 19981208

AB The invention relates to a process for obtaining L-dihydroorotic acid by chromatog. on an anionic exchange material in a base water mixt. under a pressure from about 1.1 MPa to about 40 MPa. The process can be used to investigate the in vitro and in vivo activity of N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide, N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrontonamide and similar compds. (dihydroorotic acid **dehydrogenase** inhibitors). The process can also be used to prep. a diagnostic assay.

IT **96187-53-0**, Brequinar
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(as L-dihydroorotic acid **dehydrogenase** inhibitor, detn. or monitoring of; anion exchange HPLC for obtaining L-dihydroorotic acid and use thereof)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



IT **96187-53-0**, Brequinar
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(as L-dihydroorotic acid **dehydrogenase** inhibitor, detn. or monitoring of; anion exchange HPLC for obtaining L-dihydroorotic acid and use thereof)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 8 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 126:139905 CA
TITLE: Methods of reducing toxicity of chemotherapeutic and antiviral agents with acylated non-methylated

pyrimidine nucleosides
INVENTOR(S): Vonborstel, Reid W.; Bamat, Michael K.
PATENT ASSIGNEE(S): Pro-Neuron, Inc., USA
SOURCE: PCT Int. Appl., 142 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640165	A1	19961219	WO 1996-US10067	19960606
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
IN 177670	A	19970215	IN 1994-CA701	19940902
US 5968914	A	19991019	US 1995-472210	19950607
AU 9661114	A1	19961230	AU 1996-61114	19960606
AU 724805	B2	20000928		
EP 831849	A1	19980401	EP 1996-918461	19960606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 10511689	T2	19981110	JP 1996-502184	19960606
AU 9952624	A1	19991202	AU 1999-52624	19991001

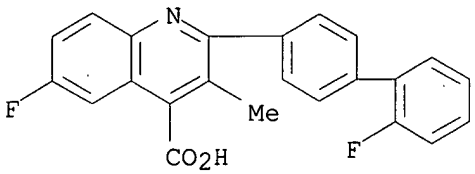
PRIORITY APPLN. INFO.:

US 1995-472210	A	19950607
US 1987-115923	B2	19871028
US 1987-115929	B2	19871028
US 1989-438493	B2	19890627
US 1990-487984	B2	19900205
US 1991-724340	B2	19910705
US 1992-903107	B2	19920625
IN 1992-CA473	A1	19920706
US 1993-61381	B2	19930514
US 1993-176485	A2	19931230
AU 1995-29150	A3	19950630
WO 1996-US10067	W	19960606

AB Compds., compns. and methods are disclosed for the treatment and prevention of toxicity due to chemotherapeutic agents and antiviral agents. Disclosed are acylated derivs. of non-methylated pyrimidine nucleosides. These compds. are capable of attenuating damage to the hematopoietic system in animals receiving antiviral or antineoplastic chemotherapy. Oral administration of triacetyluridine ameliorated the hematol. toxicity of 5-fluorouracil. Triacetyluridine and uridine increased the therapeutic index of 5-fluorouracil in tumor-bearing mice. Amelioration of the adverse effects of e.g. AZT is also described.

IT **96187-53-0**, Brequinar
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acylated pyrimidine nucleosides, alone or in combination with other compds., for reducing toxicity of chemotherapeutic and antiviral agents)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)

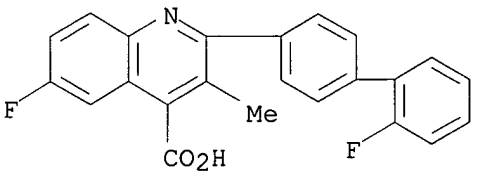


IT **96187-53-0**, Brequinar
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acylated pyrimidine nucleosides, alone or in combination with other compds., for reducing toxicity of chemotherapeutic and antiviral agents)

L17 ANSWER 5 OF 8 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 119:85643 CA
TITLE: Enhancement of allograft survival by combination RS-61443 and DUP-785 therapy
AUTHOR(S): Kawamura, Takashi; Hullett, Debra A.; Suzuki, Yasuyuki; Bechstein, Wolf O.; Allison, Anthony M.; Sollinger, Hans W.
CORPORATE SOURCE: Dep. Surg., Univ. Wisconsin, Madison, WI, USA
SOURCE: Transplantation (1993), 55(4), 691-5
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Current maintenance immunosuppressive therapy consists of cyclosporine in combination with prednisone and azathioprine. Unfortunately these agents are assocd. with significant side effects resulting in post-transplant morbidity and mortality. Therefore, the search for new immunosuppressive agents is essential, not only to improve the results after organ transplantation but equally important to reduce morbidity. Recently two new antiproliferative drugs, RS-61443 (RS) and DUP-785 (DUP), have become available. RS (mycophenolate mefotil), a semisynthetic deriv. of mycophenolic acid, inhibits purine de novo synthesis by noncompetitively and reversibly inhibiting inosine monophosphate **dehydrogenase**. DUP (brequinar sodium) inhibits pyrimidine synthesis by reversibly inhibiting dehydroorotate **dehydrogenase**. The authors evaluated subtherapeutic combination RS and DUP therapy in the rat (ACI.fwdarw.LEW) heterotopic heart allograft model. Median graft survival with no treatment, RS (20 mg/kg/day), DUP 3 mg/kg (3.times./wk), or DUP 6 mg/kg (3.times./wk) was 6.5, 11.5, 9.5 and 14.5, resp. Median graft survival with combination therapy (RS 20 mg/kg, DUP 6 or 3 mg/kg 3.times./wk) was 133 days and 121 days, resp. Furthermore, mean survival following cessation of all therapy at 100 days post-transplant was dramatically prolonged to 65.7 .+-. 43.8 days in animals receiving combination therapy (RS 20 mg/kg/day, DUP 6 mg/kg 3.times./wk). Despite the potent immunosuppressive activity, recipients treated with combination therapy demonstrated no side effects and gained body wt. during the treatment. To det. if low-dose combination therapy was effective in reversing ongoing rejection, treatment was delayed until the 5th postoperative day. Four of 5 recipients (80%) receiving RS monotherapy (60 mg/kg/day), 5 of 5 recipients (100%) receiving DUP monotherapy (12 mg/kg/day), and 4 of 5 grafts (80%) receiving combination therapy (RS 40 mg/kg/day and DUP 6 mg/kg/day) survived over 21 days. The authors results demonstrate that combination therapy significantly prolonged graft survival, and that the progression of advanced rejection was halted immediately. RS and DUP combination may provide a potent immunosuppressive therapy in clin. transplantation.

IT **96201-88-6**, DUP-785
RL: BIOL (Biological study)
(heart allograft survival increase by RS61443 and, immunosuppression in)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, DUP-785
RL: BIOL (Biological study)
(heart allograft survival increase by RS61443 and, immunosuppression in)

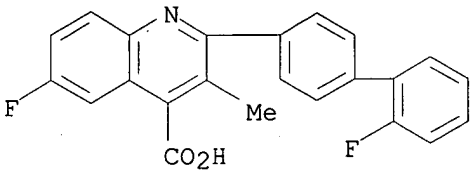
L17 ANSWER 6 OF 8 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 113:108893 CA
TITLE: In vivo inhibition of the pyrimidine de novo enzyme dihydroorotic acid **dehydrogenase** by Brequinar sodium (DUP-785; NSC 368390) in mice and patients
AUTHOR(S): Peters, G. J.; Schwartsmann, G.; Nadal, J. C.; Laurensse, E. J.; Van Groeningen, C. J.; Van der Vijgh, W. J. F.; Pinedo, H. M.
CORPORATE SOURCE: Dep. Oncol., Free Univ. Hosp., Amsterdam, 1007 MB, Neth.
SOURCE: Cancer Research (1990), 50(15), 4644-9
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In mice a new inhibitor of dihydroorotic acid **dehydrogenase** (DHO-DH), Brequinar sodium (DUP-785, NSC 368390) depleted the plasma uridine concn. to 40% within 2 h, followed by a small rebound after 7-9 days. The drug was subsequently evaluated in a Phase I clin. trial, during which it was possible to follow its biochem. effects in 24 patients (27 courses). In addn. to the measurement of plasma uridine concns., the authors also measured in lymphocytes of 9 patients (10 courses) the duration of DHO-DH inhibition. Brequinar sodium was administered every 3 wk as an i.v. infusion at dose levels of 15-2250 mg/m2. The biochem. effects were studied following the first administration of the drug. In sonicated exts. of lymphocytes from 7 healthy volunteers the activity of DHO-DH varied from 2.0 to 3.9 nmol/h per 106 cells, while in the lymphocytes of 9 patients obtained immediately before treatment this value was between 0.5 and 4.8 nmol/h per 106 cells. Within 15 min of drug administration DHO-DH activity was not detectable and was still low up to 1 wk later. Duration of the inhibition appeared to be related to the extent of clin. toxicity, e.g., myelosuppression, nausea, vomiting, diarrhea, and mucositis. Severe lymphopenia was obsd. in patients receiving Brequinar sodium at the max. tolerated dose. At dose levels of .gtoreq.600 mg/m2, uridine depletion (40-85%) was obsd. between 6 h and 4

days, followed by a rebound of 160-350% after 4-7 days. The extent of the depletion and of the accompanying rebound of uridine levels and the extent and duration of DHO-DH inhibition in the individual patients could be partially assocd. with drug toxicity in these patients. This is the first report describing biol. effects of DHO-DH inhibition in humans in relation to the degree and duration of inhibition of this enzyme.

IT **96201-88-6**, NSC 368390
RL: BIOL (Biological study)
(dihydroorotic acid **dehydrogenase** inhibition by)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, NSC 368390
RL: BIOL (Biological study)
(dihydroorotic acid **dehydrogenase** inhibition by)

L17 ANSWER 7 OF 8 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 112:171892 CA

TITLE: Antitumor activity of Brequinar sodium (Dup-785) against human head and neck squamous cell carcinoma xenografts

AUTHOR(S): Braakhuis, B. J. M.; Van Dongen, G. A. M. S.; Peters, G. J.; Van Walsum, M.; Snow, G. B.

CORPORATE SOURCE: Dep. Otolaryngol., Free Univ. Hosp., Amsterdam, 1081 HV, Neth.

SOURCE: Cancer Letters (Shannon, Ireland) (1990), 49(2), 133-7
CODEN: CALEDQ; ISSN: 0304-3835

DOCUMENT TYPE: Journal

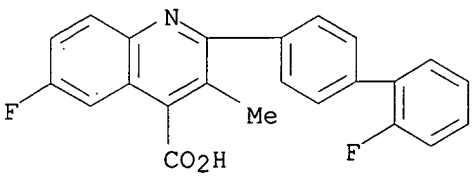
LANGUAGE: English

AB The effect of Brequinar sodium on the growth of xenografts established from head and neck squamous cell carcinomas (HNSCC) was assessed. Brequinar sodium is a novel drug, known to inhibit dihydroorotic acid **dehydrogenase** (DHO-DH), resulting in a decrease of the pyrimidine de novo synthesis. The drug was administered i.p. to tumor-bearing nude mice, once a day, during 5 days at a max. tolerated dose of 50 mg/kg. The growth-delaying effects were obsd. in 4 out of 5 lines tested. In 3 of these lines the effect was moderate and short lasting, whereas in one line (HNX-LP) tumor growth rate was totally inhibited for a 17-day period. In this line, Brequinar sodium was superior to 5 drugs known to be active in HNSCC patients. In two tumor lines DHO-DH activity could be measured and the results are in agreement with the concept that there is a relation between Brequinar sodium sensitivity and enzyme activity.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(squamous cell carcinomas inhibitions by, in human head and neck xenografts)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



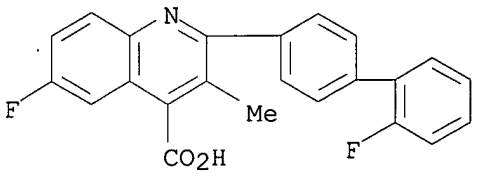
IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(squamous cell carcinomas inhibitions by, in human head and neck xenografts)

L17 ANSWER 8 OF 8 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 112:91373 CA
TITLE: Retention of in vivo antipyrimidine effects of brequinar sodium (DUP-785; NSC 368390) in murine liver, bone marrow and colon cancer
AUTHOR(S): Peters, G. J.; Nadal, J. C.; Laurensse, E. J.; De Kant, E.; Pinedo, H. M.
CORPORATE SOURCE: Dep. Oncol., Free Univ. Hosp., Amsterdam, 1007 MB, Neth.
SOURCE: Biochemical Pharmacology (1990), 39(1), 135-44
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Brequinar sodium (DUP-785) is a potent inhibitor of the pyrimidine de novo enzyme, dihydroorotic acid **dehydrogenase** (DHO-DH). In order to det. whether in vitro data could be extrapolated to the in vivo situation, the antipyrimidine effects of DUP-785 were examd. in mice bearing colon cancer. Two tumor models were used, Colon 26 and Colon 38 which are resistant and moderately sensitive, resp., to DUP-785. DUP-785 at 50 mg/kg caused a depletion of plasma uridine in mice, and depleted tissue uridine levels in Colon 38 down to 10%, which was sustained for several days; in Colon 26, the decrease was less and tissue uridine levels recovered rapidly. In the livers of these mice, no significant effect on uridine was obsd. DUP-785 depleted UTP in bone marrow cells within 2 h to 25% of control levels; after 4 days, normal levels were found. In livers of both Balb-c mice (bearing Colon 26) and C57BI/6 mice (bearing Colon 38), a small decrease of uridine nucleotide pools was found. In Colon 26, DUP-785 increased uridine nucleotide pools to 170% after 2 h; at 1 day, normal levels were obsd., but after 2 days, an increase was found again. In Colon 38 DUP-785 decreased the uridine nucleotide pool by 50% after 1 and 2 days. DUP-785 did not affect cytidine nucleotide pools of liver and of Colon 26 and Colon 38. The ratio between uridine nucleotides and cytidine nucleotides decreased from 2.2 to 0.90 in Colon 38; in the other tissues, the decrease was less. DHO-DH was measured in bone marrow cells and Colon 26 and 38 before and after treatment. Basal levels of DHO-DH were 3 times higher in Colon 26 than in Colon 38. In treated tumors, DHO-DH was initially inhibited by more than 90%; after 7 days enzyme activity in Colon 26 was 50% and in Colon 38 about 200% of basal levels. In bone marrow cells, DHO-DH was also rapidly inhibited, but recovered to normal levels within 4 days. It is concluded that the retention of antipyrimidine effects of DUP-785 in Colon 38 were more pronounced than in Colon 26, which is in agreement with the better antitumor effect of DUP-785 in Colon 38.

IT **96201-88-6**, NSC 368390

RL: PRP (Properties)
(antipyrimidine effects of, in bone marrow and colon cancer and liver)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

IT **96201-88-6**, NSC 368390
RL: PRP (Properties)
(antipyrimidine effects of, in bone marrow and colon cancer and liver)

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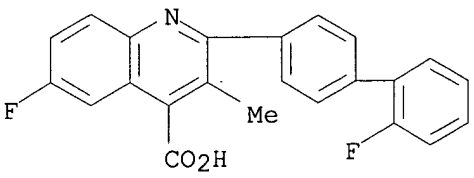
L20 ANSWER 1 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 138:390922 CA
TITLE: Arsenide compound system for selective targeting of apoptotic cells
INVENTOR(S): Hogg, Philip John
PATENT ASSIGNEE(S): Unisearch Limited, Australia
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039564	A1	20030515	WO 2002-AU1523	20021108

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: AU 2001-8746 A 20011108
OTHER SOURCE(S): MARPAT 138:390922
AB The invention discloses a method of selectively targeting an active agent (or agent capable of becoming an active agent) to apoptotic cells in a vertebrate, comprising administering to the vertebrate a system comprising an arsenoxide (or arsenoxide equiv.) compd. and the agent, wherein the system selectively targets apoptotic cells. Prepn. of e.g. 4-[N-(S-glutathionylacetyl)amino]phenylarsenoxide is described.

IT **96187-53-0**, Brequinar
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arsenide compd. system for selective targeting of apoptotic cell)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 137:231367 CA
TITLE: Anti-CD2 antibodies or CD2 antagonists and immunomodulating agents for preventing or treating inflammatory or autoimmune disorders
INVENTOR(S): Dingivan, Christine
PATENT ASSIGNEE(S): Medimmune, Inc., USA
SOURCE: PCT Int. Appl., 189 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002069904	A2	20020912	WO 2002-US6761	20020304
WO 2002069904	A3	20030220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-273098P P 20010302
US 2001-346918P P 20011019

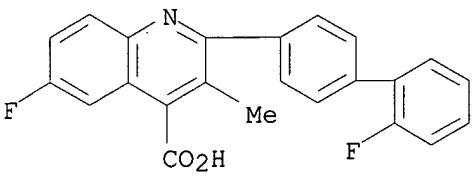
AB The present invention provides to methods of preventing, treating or ameliorating an autoimmune or inflammatory disorder or one or more symptoms thereof utilizing combinatorial therapy. In particular, the present invention provides methods of preventing, treating, or ameliorating an autoimmune or inflammatory disorder or one or more symptoms thereof comprising administering to a subject in need thereof one or more CD2 antagonists and at least one other prophylactic or therapeutic agent. The present invention also provides compns. and articles of manuf. for use in preventing, treating or ameliorating one or more symptoms assocd. with an autoimmune or inflammatory disorder.

IT **96187-53-0**, Brequinar
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(anti-CD2 antibodies or CD2 antagonists and immunomodulating agents for preventing or treating inflammatory or autoimmune disorders)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 3 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 134:331600 CA

TITLE: Use of a CD40:CD154 binding interruptor to treat immunological complications of the eye

INVENTOR(S): Dana, M. Reza; Vaishnaw, Akshay K.; Burkly, Linda C.; Lobb, Roy; Adelman, Burt

PATENT ASSIGNEE(S): Biogen, Inc., USA; Schepens Eye Research Institute

SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030386	A1	20010503	WO 2000-US28945	20001019
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1223981	A1	20020724	EP 2000-973678	20001019
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003512439	T2	20030402	JP 2001-532803	20001019
US 2003027744	A1	20030206	US 2002-125264	20020418

PRIORITY APPLN. INFO.:

US 1999-160909P	P	19991022
US 2000-196453P	P	20000411
US 2000-229491P	P	20000831
WO 2000-US28945	W	20001019

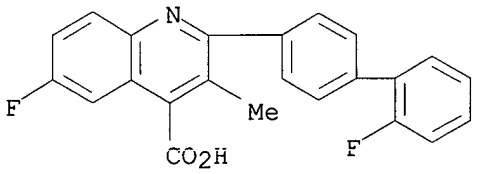
AB The invention relates generally to the treatment and **inhibition** of immunol. complications of the eye. Such complications include unwanted immune responses resulting in an ocular inflammatory disease, resulting from a corneal or retinal graft transplantation or resulting from ocular angiogenesis, particularly ocular neovascularization. The invention relates in particular to the **inhibition**, treatment, or reversal of immune-system driven rejection of grafted corneal or retinal tissue or cells in a recipient host and to the treatment or **inhibition** of ocular inflammatory disease or ocular neovascularization in a host. Compns. and methods disclosed herein capitalize on the discovery that

immunol. complications of the eye can be **inhibited** using a CD40:CD154 binding interruptor, either alone or in combination with another immunomodulator or immunosuppressor. An exemplary CD40:CD154 binding interruptor is an anti-CD154 monoclonal antibody, such as an antibody having the antigen-specific binding characteristics of the 5c8 monoclonal antibody.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(use of a CD40:CD154 binding interruptor to treat immunol. complications of the eye)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



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REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

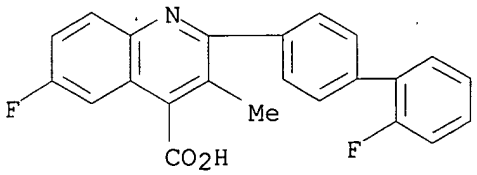
L20 ANSWER 4 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 134:187949 CA
TITLE: Brequinar in combination with cyclosporine A **inhibits** islet xenograft rejection for up to 24 days: a study in the pig-to-rat model
AUTHOR(S): Wennberg, L.; Song, Z.; Wijkstrom, M.; Zhang, J.; Bari, S.; Sundberg, B.; Groth, C. G.; Korsgren, O.
CORPORATE SOURCE: Karolinska Institute, Department of Transplantation Surgery, Huddinge Hospital, Huddinge, Swed.
SOURCE: Transplantation Proceedings (2000), 32(5), 1026
CODEN: TRPPA8; ISSN: 0041-1345
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fetal porcine islets transplanted into untreated rats are destroyed within 5 to 6 days. A study was conducted to investigate the efficacy of Brequinar in **inhibiting** islet xenograft rejection in this model. Results indicated that Brequinar in combination with cyclosporine A **inhibited** islet xenograft rejection in the pig-to-rat model for .ltoreq.24 days after transplantation. Every other day dosing and tapering of dose was applied to reduce Brequinar toxicity.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant brequinar in combination with cyclosporine A **inhibits** islet xenograft rejection for up to 24 days in pig-to-rat model)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



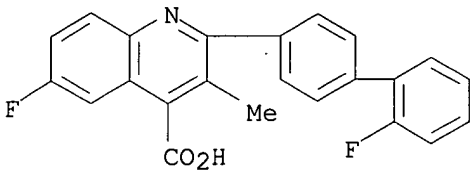
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 133:217357 CA
TITLE: Characterization of anticancer agents by their growth **inhibitory** activity and relationships to mechanism of action and structure
AUTHOR(S): Keskin, Ozlem; Bahar, Ivet; Jernigan, Robert L.; Beutler, John A.; Shoemaker, Robert H.; Sausville, Edward A.; Covell, David G.
CORPORATE SOURCE: Chemical Engineering Department and Polymer Research Center, TUBITAK Advanced Polymeric Materials Research Center, Bogazici University, Istanbul, 80815, Turk.
SOURCE: Anti-Cancer Drug Design (2000), 15(2), 79-98
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An anal. of the growth **inhibitory** potency of 122 anticancer agents available from the National Cancer Institute anticancer drug screen is presented. Methods of singular value decompn. (SVD) were applied to det. the matrix of distances between all compds. These SVD-derived dissimilarity distances were used to cluster compds. that exhibit similar tumor growth **inhibitory** activity patterns against 60 human cancer cell lines. Cluster anal. divides the 122 std. agents into 25 statistically distinct groups. The first eight groups include structurally diverse compds. with reactive functionalities that act as DNA-damaging agents while the remaining 17 groups include compds. that **inhibit** nucleic acid biosynthesis and mitosis. Examn. of the av. activity patterns across the 60 tumor cell lines reveals unique "fingerprints" assocd. with each group. A diverse set of structural features are obsd. for compds. within these groups, with frequent occurrences of strong within-group structural similarities. Clustering of cell types by their response to the 122 anticancer agents divides the 60 cell types into 21 groups. The strongest within-panel groupings were found for the renal, leukemia and ovarian cell panels. These results contribute to the basis for comparisons between log(GI50) screening patterns of the 122 anticancer agents and addnl. tested compds.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(characterization of anticancer agents by growth **inhibitory** activity and relationships to mechanism of action and structure)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



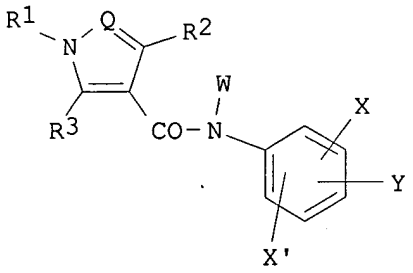
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 133:177164 CA
TITLE: Preparation of pyrazolecarboxamides and pyrrolecarboxamides as **inhibitors** of the proliferation of activated lymphocytes and as remedies for autoimmune disease.
INVENTOR(S): Ushio, Hiroyuki; Ishibuchi, Seigo; Naito, Youichiro; Sugiyama, Naoki; Kawaguchi, Takafumi; Chiba, Kenji; Ohtsuki, Makio; Naka, Yoichi
PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 315 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

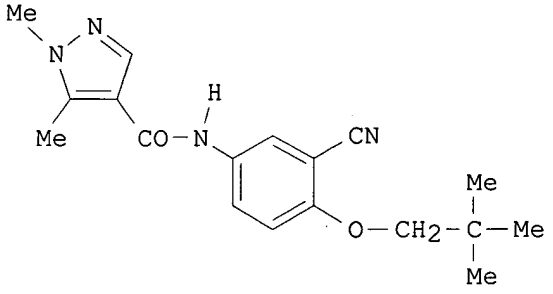
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047558	A1	20000817	WO 2000-JP767	20000210
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
NZ 514095	A	20010928	NZ 2000-514095	20000210
EP 1176140	A1	20020130	EP 2000-902925	20000210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008173	A	20021022	BR 2000-8173	20000210
JP 3419395	B2	20030623	JP 2000-598479	20000210
JP 2003176273	A2	20030624	JP 2002-375683	20000210

PRIORITY APPLN. INFO.:
JP 1999-33367 A 19990210
JP 1999-198473 A 19990713
JP 2000-598479 A3 20000210
WO 2000-JP767 W 20000210

OTHER SOURCE(S): MARPAT 133:177164
GI



I



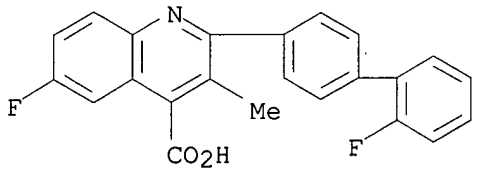
II

AB The title compds. I [R1 represents substituted aryl, heteroaryl, etc.; R2 and R3 represent each hydrogen, alkyl, halogeno, hydroxy, etc.; Q represents N, CH, etc.; W represents hydrogen, alkyl, hydroxycarbonylalkyl, etc.; X represents halogeno, cyano, nitro, amino, etc.; X' represents hydrogen, halogeno, cyano or nitro; and Y represents alkyl, hydroxy, alkoxy, etc.] are prepd. For example, pyrazolecarboxamide deriv. II was prepd. The title compds. are said to show significant **inhibiting** activity against the proliferation of activated lymphocytes in in vitro tests. A formulation is given.

IT **96201-88-6**, Brequinar sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug combination including pyrazolecarboxamides and pyrrolecarboxamides and other agents)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 133:100386 CA
TITLE: A gene expression database for the molecular

pharmacology of cancer

AUTHOR(S): Scherf, Uwe; Ross, Douglas T.; Waltham, Mark; Smith, Lawrence H.; Lee, Jae K.; Tanabe, Lorraine; Kohn, Kurt W.; Reinhold, William C.; Myers, Timothy G.; Andrews, Darren T.; Scudiero, Dominic A.; Eisen, Michael B.; Sausville, Edward A.; Pommier, Yves; Botstein, David; Brown, Patrick O.; Weinstein, John N.

CORPORATE SOURCE: Laboratory of Molecular Pharmacology, Division of Basic Sciences, National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD, USA

SOURCE: Nature Genetics (2000), 24(3), 236-244
CODEN: NGENEC; ISSN: 1061-4036

PUBLISHER: Nature America

DOCUMENT TYPE: Journal

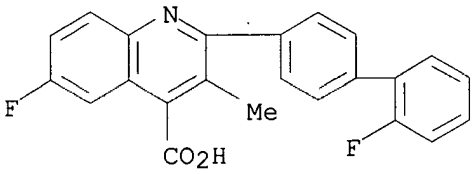
LANGUAGE: English

AB We used cDNA microarrays to assess gene expression profiles in 60 human cancer cell lines used in a drug discovery screen by the National Cancer Institute. Using these data, we linked bioinformatics and chemoinformatics by correlating gene expression and drug activity patterns in the NCI60 lines. Clustering the cell lines on the basis of gene expression yielded relationships very different from those obtained by clustering the cell lines on the basis of their response to drugs. Gene-drug relationships for the clin. agents 5-fluorouracil and L-asparaginase exemplify how variations in the transcript levels of particular genes relate to mechanisms of drug sensitivity and resistance. This is the first study to integrate large databases on gene expression and mol. pharmacol.

IT **96201-88-6**, DUP785
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(human cancer cell line gene expression database for the mol. pharmacol. of cancer)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 133:38237 CA

TITLE: Formulation with an improved therapeutic range, containing nucleotide synthesis **inhibitors**

INVENTOR(S): Lindner, Juergen; Haase, Burkhard

PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany

SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000033876	A1	20000615	WO 1999-EP9380	19991201
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19857009	A1	20000615	DE 1998-19857009	19981210
BR 9916006	A	20010904	BR 1999-16006	19991201
EP 1137438	A1	20011004	EP 1999-961041	19991201
EP 1137438	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 218370	E	20020615	AT 1999-961041	19991201
EE 200100305	A	20020815	EE 2001-305	19991201
JP 2002531525	T2	20020924	JP 2000-586366	19991201
ES 2178496	T3	20021216	ES 1999-961041	19991201
BG 105548	A	20011231	BG 2001-105548	20010530
NO 2001002719	A	20010601	NO 2001-2719	20010601
HR 2001000429	A1	20020630	HR 2001-429	20010607

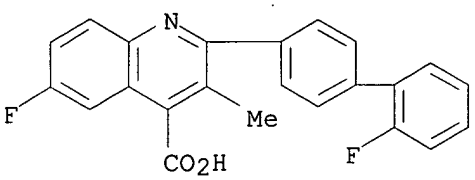
PRIORITY APPLN. INFO.: DE 1998-19857009 A 19981210
WO 1999-EP9380 W 19991201

OTHER SOURCE(S): MARPAT 133:38237

AB The therapeutic range of nucleotide synthesis **inhibitors** (NSI) administered to treat immunol. diseases or cancer or for transplantation is increased by (a) interrupting the enterohepatic circulation of NSI (e.g. by orally administering an ion exchanger such as cholestyramine) and/or (b) subsequently administering, after a suitable interval, an antagonist of NSI (e.g. a purine or pyrimidine nucleotide). The action of the agents under (a) and (b) is based on the fact that the desired action of NSI on the immune system is achieved rapidly and is not enhanced by further exposure, whereas side effects of NSI increase during longer residence in the circulation. Thus, rats with adjuvant-induced arthritis were orally administered N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide (2.5 mg/kg/day) and cholestyramine (1000 mg/kg/day) for 17 days to produce a decrease in arthritis index of 92%.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation with improved therapeutic range contg. nucleotide synthesis **inhibitors**)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



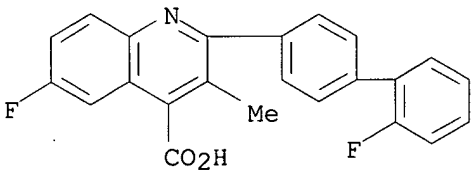
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 131:27623 CA
TITLE: FK 506 prevents islet xenograft rejection: a study in the pig-to-rat model
AUTHOR(S): Song, Z.; Wennberg, L.; Bennet, W.; Sundberg, B.; Groth, C. G.; Korsgren, O.
CORPORATE SOURCE: Department of Transplantation Surgery, Huddinge Hospital, Huddingeand, 141 86, Swed.
SOURCE: Transplantation Proceedings (1999), 31(1/2), 981 CODEN: TRPPA8; ISSN: 0041-1345
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to investigate the efficacy of FK 506 in preventing islet xenograft rejection in the pig-to-rat model. FK 506 alone **inhibited** xenograft rejection in the pig-to-rat model. FK 506 in combination with prednisolone or rapamycin had no or only marginal effect on the rejection. When FK 506 was combined with cyclophosphamide or 15-deoxyspergualin, an **inhibitory** effect was obsd. FK 506 in combination with brequinar almost completely **inhibited** rejection. There were no side effects obsd. in each group.

IT **96187-53-0**, Brequinar
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prevention of islet xenograft rejection in the pig-to-rat model by FK 506)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 10 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 130:232486 CA
TITLE: Compositions and methods for preventing and treating allograft rejection
INVENTOR(S): Bennett, C. Frank; Stepkowski, Stanislaw M.

PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA; Board of Regents, the University of Texas System
SOURCE: U.S., 41 pp., Cont.-in-part of U.S. 5,514,788.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 22
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5883082	A	19990316	US 1994-344155	19941123
US 5591623	A	19970107	US 1993-7997	19930121
US 5514788	A	19960507	US 1993-63167	19930517
WO 9615780	A1	19960530	WO 1995-US15536	19951122
W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9643712	A1	19960617	AU 1996-43712	19951122

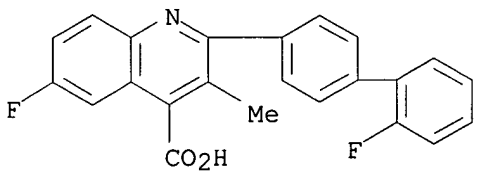
PRIORITY APPLN. INFO.:

US 1990-567286	B2	19900814
US 1992-939855	B2	19920902
US 1993-7997	A2	19930121
US 1993-63167	A2	19930517
US 1994-334155	A2	19941123
US 1994-344155	A	19941123
WO 1995-US15536	W	19951122

AB Compns. and methods for preventing and treating allograft rejection comprise an antisense oligonucleotide targeted to a nucleic acid sequence encoding intercellular adhesion mol.-1 (ICAM-1), vascular cell adhesion mol.-1 (VCAM-1), or endothelial leukocyte adhesion mol.-1 (ELAM-1) in combination with an immunosuppressive agent (e.g. monoclonal antibody, rapamycin, brequinar, cyclosporin A, or anti-lymphocyte serum). Hearts from Lewis rats were transplanted into ACI rats. Control rats (no treatment) had a mean graft survival time of 8.8 .+-. 0.8 days. Rats treated with oligonucleotide ISIS 9125 (5 and 10 mg/kg for 7 days) had a mean graft survival time of 10 .+-. 3.0 and 18 .+-. 3.8 days, resp. However, rats treated with both cyclosporin A (4 mg/kg for 7 days) and ISIS 9125 (10 mg/kg for 7 days) had a mean graft survival time of 21.7 .+-. 7.4 days.

IT **96187-53-0**, Brequinar
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-treatment with; compns. and methods for preventing and treating allograft rejection)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 11 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 130:24115 CA
TITLE: Use of a CD40:CD154 binding interrupter to prevent counter adaptive immune responses, particularly graft rejection
INVENTOR(S): Kirk, Allan D.; Harlan, David M.; Thomas, David; Kauffman, Michael; Burkly, Linda
PATENT ASSIGNEE(S): Biogen, Inc., USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9852606	A1	19981126	WO 1998-US10075	19980515
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9874940	A1	19981211	AU 1998-74940	19980515
AU 735592	B2	20010712		
EP 980259	A1	20000223	EP 1998-922381	19980515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EE 9900528	A	20000615	EE 1999-528	19980515
BR 9809641	A	20000711	BR 1998-9641	19980515
NZ 500974	A	20010629	NZ 1998-500974	19980515
JP 2002500648	T2	20020108	JP 1998-550477	19980515
WO 9856417	A1	19981217	WO 1998-US11910	19980610
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9879567	A1	19981230	AU 1998-79567	19980610
AU 748533	B2	20020606		
EP 1009432	A1	20000621	EP 1998-930097	19980610
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002504120	T2	20020205	JP 1999-503086	19980610
NO 9905617	A	20000117	NO 1999-5617	19991116
MX 9910571	A	20000731	MX 1999-10571	19991117
MX 9910893	A	20000430	MX 1999-10893	19991125
US 2002119150	A1	20020829	US 2002-120272	20020409

PRIORITY APPLN. INFO.:

US 1997-46791P	P	19970517
US 1997-49389P	P	19970611
US 1998-85145P	P	19980512
WO 1998-US10075	W	19980515

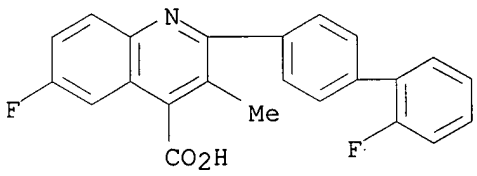
WO 1998-US11910 W 19980610
US 1999-442012 B1 19991117

AB Compns. and methods disclosed herein capitalize on the discovery that rejection of a tissue graft can be **inhibited** using a CD40:CD154 binding interrupter, either alone or in combination with another immunomodulator or immunosuppressor. An advantageous, synergistic combination includes a CD40:CD154 binding interrupter and a CD28 signalling interrupter. An exemplary CD40:CD154 binding interrupter is an anti-CD154 monoclonal antibody, such as an antibody having the antigen-specific binding characteristics of the 5c8 monoclonal antibody. An exemplary CD28 signalling interrupter is a CTLA4-Ig fusion protein. The disclosed compns. and methods unexpectedly can be used to prolong survival of grafted tissue in a recipient host, to reverse acute graft rejection, and to attenuate immunol. consequences of the failure of grafted tissue.

IT **96201-88-6**, Brequinar sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of a CD40/CD154 binding interrupter to prevent counter adaptive immune responses or particularly graft rejection)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 12 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 129:260351 CA
TITLE: Preparation and formulation of 2-aryl-4-quinolinecarboxamides and analogs as calpain **inhibitors**
INVENTOR(S): Daines, Robert A.; Kingsbury, William D.; Pendrak, Israil; Mallamo, John P.
PATENT ASSIGNEE(S): Smithkline Beecham Corp., USA; Cephalon, Inc.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9841506	A1	19980924	WO 1998-US4874	19980313
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 983243	A1	20000308	EP 1998-910350	19980313
R: BE, CH, DE, ES, FR, GB, IT, LI, NL				

JP 2001515509	T2	20010918	JP 1998-540630	19980313
US 6100267	A	20000808	US 1999-380318	19990830

PRIORITY APPLN. INFO.: US 1997-40583P P 19970314
WO 1998-US4874 W 19980313

OTHER SOURCE(S): MARPAT 129:260351

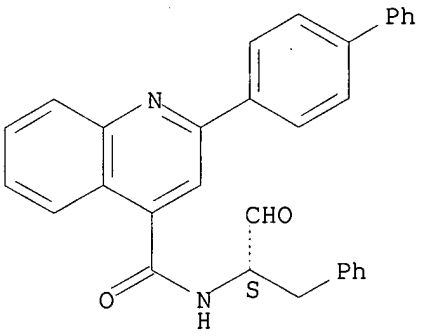
AB R4Z1ZCONHCHRR5 [I; R = CH2Ph, (CH2)4NR1R3, CH2CHMe2, etc.; R1 = CO2CH2Ph, SO2Me, arylsulfonyl, etc.; R3 = H, Me, alkyl; R4 = H when Z1 = arylene; otherwise R4 = Ph, pyridyl, etc.; R5 = CHO, COCH2F, COCO2H, etc.; Z = 2,4-naphthylene or 2,4-quinolinediyl; Z1 = arylene, C.tplbond.C, piperazine-1,4-diyl] were prepd. Thus, 2-phenyl-4-quinolinecarboxylic acid was amidated by (S)-H2NCH(CH2Ph)CH2OH and the product oxidized to give (S)-PhZCONHCH(CH2Ph)CHO (Z = 2,4-quinolinediyl). Data for biol. activity of I were given.

IT **213482-73-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of 2-aryl-4-quinolinecarboxamides and analogs as calpain **inhibitors**)

RN 213482-73-6 CA

CN 4-Quinolinecarboxamide, 2-[1,1'-biphenyl]-4-yl-N-[(1S)-1-formyl-2-phenylethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 13 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 129:260343 CA

TITLE: Preparation of tetracyclic quinoline derivatives as immunosuppressants.

INVENTOR(S): Chujou, Iwao; Masuda, Yoshiaki; Fujino, Kenji; Kato, Yukiko; Ogasa, Takehiro; Kasai, Seiji; Nakajima, Hiroshi; Nakazato, Nobuhiro

PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 20 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

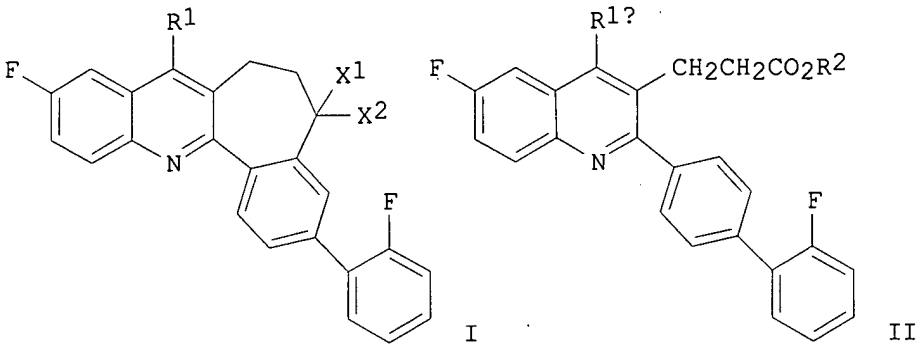
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10231289	A2	19980902	JP 1997-333776	19971204

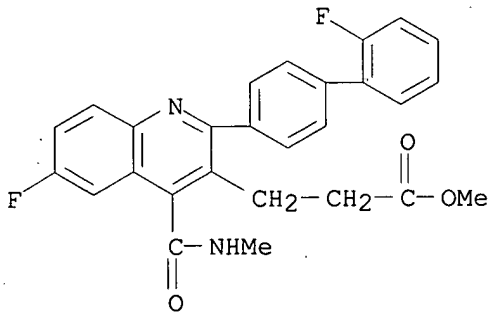
PRIORITY APPLN. INFO.: JP 1996-326603 19961206
JP 1996-341051 19961220
OTHER SOURCE(S): CASREACT 129:260343; MARPAT 129:260343
GI



AB The title benzo[6,7]cyclohepta[1,2-b]quinoline derivs. [I; R1 = CO2H, CHO, CONR3R4, CO2R5, CH2Z; wherein R3, R4 = H, C1-18 alkyl, (un)substituted aryl or aralkyl or NR3R4 = heterocyclyl; R5 = C1-4 alkyl, (un)substituted aralkyl; Z = halo, HO; X1 = H, HO; X2 = H or X1 and X2 are combined together represent O; provided that when X1 = CO2H, X1 and X2 are not simultaneously H] are prepd. by cyclization of 3-(2-biphenylylquinolin-3-yl)propanoic acid derivs. [II; R1a = CONR3R4, CH2Z; R3, R4, Z = same as above; R2 = H, C1-4 alkyl, (un)substituted aralkyl] under Friedel-Crafts reaction conditions. Thus, I (R1a = CONHMe, R2 = H) (prepn. given) was dissolved in CF3SO3H and heated with stirring for 5 h at 120.degree. to give 18% I (R1 = CONHMe, X1X2 = O). I [R1 = CONH(CH2)7Me, X1 = X2 = H] **inhibited** 51.3% plaque-forming cell (PFC) from spleen of mouse sensitized by sheet red blood cells.

IT **213540-74-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of tetracyclic quinoline derivs. as immunosuppressants by cyclization of (biphenylylquinolinyl)propanoic acid derivs. under Friedel-Crafts conditions)

RN 213540-74-0 CA
CN 3-Quinolinepropanoic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-4-[(methylamino)carbonyl]-, methyl ester (9CI) (CA INDEX NAME)



L20 ANSWER 14 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 129:160642 CA

TITLE: Tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue
INVENTOR(S): Thall, Aron
PATENT ASSIGNEE(S): Biotransplant, Inc., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

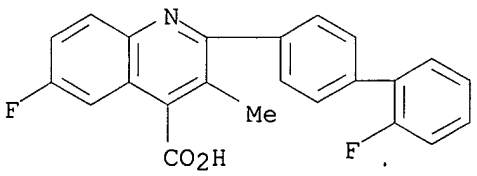
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9833528	A2	19980806	WO 1998-US2103	19980205
WO 9833528	A3	19990211		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9863191	A1	19980825	AU 1998-63191	19980205
EP 969872	A2	20000112	EP 1998-907366	19980205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001518074	T2	20011009	JP 1998-533214	19980205

PRIORITY APPLN. INFO.: US 1997-795925 A 19970205
WO 1998-US2103 W 19980205

AB The invention provides methods and compns. for promoting in a first species a state of tolerance against Gal.alpha.1,3Gal epitopes present on a xenograft from a second species, thereby preventing hyperacute rejection (HAR) of the xenograft. In a first aspect, the invention provides methods and tolerogenic compns. for inducing anergy in B-cells specific for the Gal.alpha.1,3Gal epitope. In a second aspect, the invention provides methods and tolerogenic compns. for inducing apoptosis in B-cells. In a third aspect, the invention provides methods and compns. for the cytotoxic elimination of memory B-cells and T-cells.

IT **96187-53-0D**, Brequinar, analogs
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 15 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 128:253012 CA
TITLE: Improved therapeutic use of 4-quinolinecarboxylic acid

derivatives, in particular brequinar, by co-administration of a pyrimidine

INVENTOR(S): Chong, Anita; Xu, Xiulong
PATENT ASSIGNEE(S): Williams, James, W., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

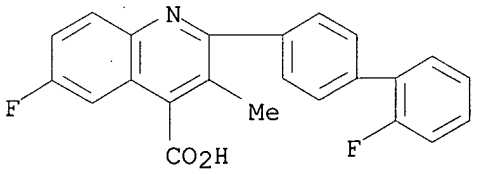
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9813047	A1	19980402	WO 1997-US17271	19970926
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9745960	A1	19980417	AU 1997-45960	19970926

PRIORITY APPLN. INFO.: US 1996-721225 19960926
WO 1997-US17271 19970926

AB Improved methods are disclosed for using 4-quinolinecarboxylic acid derivs., particularly brequinar, for the treatment of various medical conditions, including cancer, arthritis, inflammatory disorders, and organ transplantation rejection. These methods improve the therapeutic effectiveness and reduce the toxicity of the 4-quinolinecarboxylic acid derivs. The improvement comprises co-administration of a pyrimidine, e.g. uridine.

IT **96187-53-0**, Brequinar
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrimidine co-administration for improved therapeutic use of quinolinecarboxylic acid derivs., esp. brequinar)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 16 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 128:123807 CA
TITLE: Method using ruthenium complexes for **inhibiting** immune response and for treating hyperproliferative vascular diseases
INVENTOR(S): Bastos, Cecilia M.; Ocain, Timothy D.
PATENT ASSIGNEE(S): Procept, Inc., USA

SOURCE: U.S., 8 pp., Cont.-in-part of U.S. Ser. No. 331,204, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5708022	A	19980113	US 1995-482308	19950607
WO 9613510	A1	19960509	WO 1995-US14067	19951030
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9540176	A1	19960523	AU 1995-40176	19951030

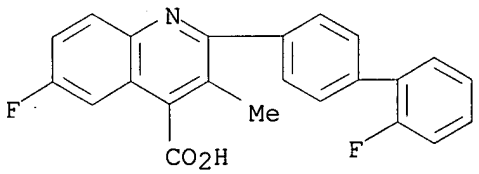
PRIORITY APPLN. INFO.:
US 1994-331204 19941028
US 1994-331388 19941028
US 1995-472525 19950607
US 1995-482308 19950607
WO 1995-US14067 19951030

OTHER SOURCE(S): MARPAT 128:123807

AB Use of ruthenium complexes as immunosuppressive agents to prevent or significantly reduce graft rejection in organ and bone marrow transplantation is described. The ruthenium complexes can also be used as immunosuppressant drugs for T-lymphocyte-mediated autoimmune diseases, e.g. diabetes, and may be useful in alleviating psoriasis and contact dermatitis. The ruthenium complexes can also be used therapeutically in the treatment of hyperproliferative vascular disease.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ruthenium complexes for **inhibiting** immune response and for treating hyperproliferative vascular diseases, and combinations with other agents)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



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REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 17 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 126:126906 CA
TITLE: Metal-containing compounds and their use for **inhibiting** the immune response
INVENTOR(S): Bastos, Cecilia M.; Ocain, Timothy D.
PATENT ASSIGNEE(S): Procept, Inc., USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640170	A2	19961219	WO 1996-US5942	19960429
WO 9640170	A3	19970213		

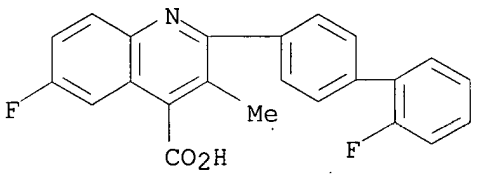
W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1995-472952 19950607
US 1995-479341 19950607

AB Use of compds. as immunosuppressive agents to prevent or significantly reduce graft rejection in organ and bone marrow transplantation is described. The compds. described herein can also be used as immunosuppressant drugs for T-lymphocyte mediated autoimmune diseases, such as diabetes, and may be useful in alleviating psoriasis and contact dermatitis. The compds. can also be used therapeutically in the treatment of hyperproliferative vascular disease and to reduce/suppress the immune response in a mammal undergoing gene therapy.

IT **96201-88-6**, Brequinar sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metal-contg. compds. as immunosuppressant for treating autoimmune diseases)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 18 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 125:184922 CA
TITLE: The significance of timing of additional short-term immunosuppression in the donor-specific transfusion/cyclosporine-treated rat
AUTHOR(S): Levy, Adam E.; Alexander, J. Wesley
CORPORATE SOURCE: Department of Surgery, University of Cincinnati Medical Center, Cincinnati, OH, 45267-0558, USA
SOURCE: Transplantation (1996), 62(2), 262-266
CODEN: TRPLAU; ISSN: 0041-1337
PUBLISHER: Williams & Wilkins

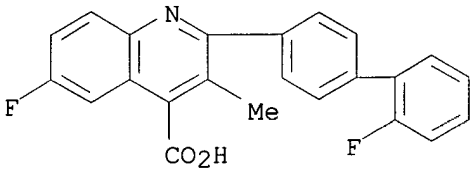
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It is hypothesized that the mechanism, or mechanisms, responsible for donor-specific transfusion (DST)/cyclosporine (CsA) immunosuppression is generated by an active immune response that is most dynamic in the immediate peritransplant period and thus might be at the peak of vulnerability to the influences of added immunosuppression. To better define this concept, four immunosuppressive drugs were combined with a d-1 DST and 14-day course of CsA in the ACI-to-Lewis cardiac transplant model. A 5-day course of antithymocyte globulin (ATG) initiated at d-1 or d+4 with DST/CsA reduced survival vs. DST/CsA alone (27.0 .+-.2.6 days and 24.6.+-.5.7 days vs. 95.3.+-.16.3 days, P<.05). Delay of initiation to d+7 improved survival to 39.5.+-.8.9 days. A 5-day course of methylprednisolone (MP) begun at d-1 with DST/CsA decreased survival vs. DST/CsA alone, 59.2.+-.10.0 days vs. 95.3.+-.16.3 days, but delay to d+4 improved survival to 110.+-.18 days, P<.05 vs. d-1. A 3-day course of brequinar (Breq) begun at d-1 with DST/CsA increased survival to 244.+-.48.6 days, while delay to d+4 reduced survival to 49.0.+-.6.7 days, P<.05 vs. d-1. Finally, a 5-day course of rapamycin (Rapa), was given with d-1 DST/CsA treatment beginning on d-1, d0, d+1, d+3, d+5, and d+7. In this instance, no significant differences in survival were found between timing groups or DST/CsA control. Together, these data support the hypothesis that DST/CsA treatment generates an active immune response that is **inhibited** by early initiation of ATG or MP, enhanced by early administration of Breq, and unchanged by early administration of Rapa.

IT **96187-53-0**, Brequinar
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of timing of addnl. short-term immunosuppression in the donor-specific transfusion/cyclosporin-treated rat cardiac allograft)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 19 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 125:105104 CA
TITLE: Compositions and methods for preventing and treating allograft rejection
INVENTOR(S): Bennett, C. Frank; Stepkowski, Stanislaw M.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA; Board of Regents, University of Texas System
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 22
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9615780	A1	19960530	WO 1995-US15536	19951122
W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5883082	A	19990316	US 1994-344155	19941123
AU 9643712	A1	19960617	AU 1996-43712	19951122

PRIORITY APPLN. INFO.:

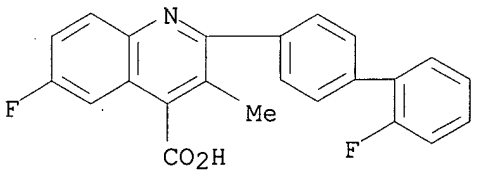
US 1994-334155	A2	19941123
US 1994-344155	A	19941123
US 1990-567286	B2	19900814
US 1992-939855	B2	19920902
US 1993-7997	A2	19930121
US 1993-63167	A2	19930517
WO 1995-US15536	W	19951122

AB Compns. and methods for preventing and treating allograft rejection comprise an antisense oligonucleotide targeted to a nucleic acid sequence encoding intercellular adhesion mol.-1 (ICAM-1), vascular cell adhesion mol.-1 (VCAM-1), or endothelial leukocyte adhesion mol.-1 (ELAM-1) in combination with an immunosuppressive agent (e.g. monoclonal antibody, rapamycin, brequinar, cyclosporin A, or anti-lymphocyte serum). Hearts from Lewis rats were transplanted into ACI rats. Control rats (no treatment) had a mean graft survival time of 8.8 .+-. 0.8 days. Rats treated with oligonucleotide ISIS 9125 (5 and 10 mg/kg for 7 days) had a mean graft survival time of 10 .+-. 3.0 and 18 .+-. 3.8 days, resp. However, rats treated with both cyclosporin A (4 mg/kg for 7 days) and ISIS 9125 (10 mg/kg for 7 days) had a mean graft survival time of 21.7 .+-. 7.4 days.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antisense oligonucleotides in combination with immunosuppressants for preventing and treating allograft rejection)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 20 OF 63 CA COPYRIGHT 2003 ACS on STN

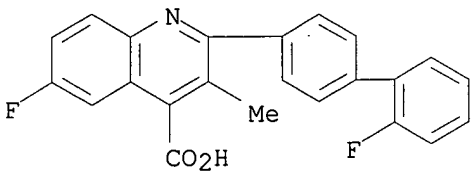
ACCESSION NUMBER:	124:219823 CA
TITLE:	Effects of leflunomide and other immunosuppressive agents on T cell proliferation in vitro
AUTHOR(S):	Chong, Anita S-F.; Rezai, Katayoun; Gebel, Howard M.; Finnegan, Alison; Foster, Preston; Xu, XiuLong; Williams, James W.
CORPORATE SOURCE:	Departments General Surgery, Rush Presbyterian St. Luke's Medical Center, Chicago, IL, 60612, USA
SOURCE:	Transplantation (1996), 61(1), 140-5 CODEN: TRPLAU; ISSN: 0041-1337

PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Leflunomide and its active metabolite, A771726, are structurally unrelated to immunosuppressive agents currently under investigation. Previous in vitro studies have revealed that leflunomide primarily **inhibits** interleukin-2-stimulated T cell proliferation. In the current study, the authors have extended the authors previous work and demonstrate that leflunomide prevents T cell progression induced by phytohemagglutinin into the S phase of the cell cycle. To discriminate further the action on T cells of leflunomide from other immunosuppressive agents, the authors performed kinetic studies where leflunomide was added either after the initiation of mixed lymphocyte cultures (MLC) or after interleukin-2 stimulation of CTLL-4 cell proliferation. These studies revealed that leflunomide acted comparably to rapamycin, but was distinct from brequinar sodium in the MLC, and distinct from cyclosporine and mycophenolic acid in both MLC and CTLL-4. Although previous biochem. studies indicated that leflunomide can **inhibit** src-family tyrosine kinase activity, more recent studies have suggested that leflunomide can also **inhibit** pyrimidine synthesis. The data demonstrate that the ability of leflunomide (25-100 .mu.M) to **inhibit** MLC and CTLL-4 cell proliferation is partially antagonized by uridine (25-100 .mu.M), and support the hypothesis that leflunomide **inhibits** pyrimidine synthesis in T cells. Unique mol. mechanisms of immunosuppression suggest that drug combinations may result in synergistic immunosuppression. The authors in vitro studies revealed synergistic **inhibition** of T cell proliferation with the combinations of leflunomide with cyclosporine or with rapamycin. The authors have extended those studies to quantitate **inhibition** of MLC by the combinations of leflunomide and brequinar sodium or mycophenolic acid.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of leflunomide and other immunosuppressive agents on T cell proliferation in vitro and use of drug combinations in relation to **inhibition** of pyrimidine synthesis)

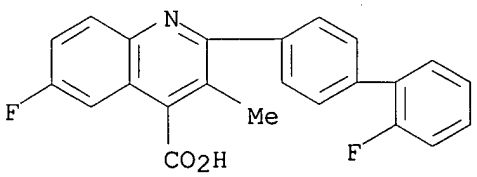
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 21 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 123:306146 CA
TITLE: Biochemical modulation of 5-fluorouracil with brequinar: Results of a phase I study
AUTHOR(S): Buzaid, Antonio C.; Pizzorno, Giuseppe; Marsh, John C.; Ravikumar, Thanjavur S.; Murren, John R.; Todd,

Mary; Strair, Roger K.; Poo, Wen-Jen; Hait, William N.
CORPORATE SOURCE: M. D. Anderson Cancer Center, University Texas, Houston, TX, 77030, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1995), 36(5), 373-8
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Biochem. modulation can increase the efficacy of 5-fluorouracil (5-FU). Pizzorno et al. have previously shown that brequinar, a de novo pyrimidine synthesis **inhibitor**, enhances the antitumor effect of 5-FU in vivo. On the basis of their data, we conducted a phase I study of brequinar in combination with 5-FU in patients with refractory solid tumors. The initial dose (100 mg/m2) of brequinar was raised in 100-mg/m2 increments in cohorts of three assessable patients. The initial dose of 5-FU was 500 mg/m2, but escalation was allowed in patients who showed no significant toxic reaction. Brequinar was administered over 1 h and 5-FU over 2 h starting 18-20 h after the initiation of infusion of brequinar. Treatments were repeated weekly. Responses were evaluated after 4 wk (one course) and then every 8 wk thereafter. Pharmacokinetics of brequinar and detn. of plasma uridine levels were performed in at least three patients at each dose level. Of the 25 patients registered in the study, 21 were assessable for toxicity studies. The dose of brequinar was escalated up to 600 mg/m2. In addn., the dose of 5-FU was increased to 600 mg/m2 as a result of a lack of a significant toxic reaction in the first nine patients. No objective responses were obsd. One patient developed grade 3 stomatitis, and one developed grade 3 esophagitis at the 400 and 600 mg/m2 dose of brequinar, resp. Brequinar produced a dose-dependent decrease in plasma uridine levels at doses up to 500 mg/m2. No addnl. decrease in plasma uridine occurred with higher doses of brequinar, thus suggesting a plateau effect. This observation prompted us to terminate the study before reaching the max. tolerated dose of brequinar. Our data indicate that brequinar in doses .gtoreq. 400 mg/m2 results in significant biochem. modulation. The lack of toxicity seen at these doses of brequinar suggests that the initial dose of the effector agent 5-FU should be increased in future studies.
IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biochem. modulation of 5-fluorouracil with brequinar in humans)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



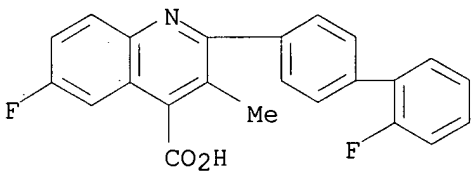
L20 ANSWER 22 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 122:306117 CA
TITLE: Effective suppression of brequinar sodium on accelerated allograft rejection in presensitized recipients

AUTHOR(S): Nozaki, S.; Ito, T.; Kamiike, W.; Uchikoshi, F.; Ito, A.; Kuhara, A.; Nakata, S.; Shirakura, R.; Miyata, M.; et al.
CORPORATE SOURCE: 1st Department Surgery, Osaka University Medical School, Suita, 565, Japan
SOURCE: Transplantation Proceedings (1995), 27(1), 451-2
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The immunosuppressant brequinar sodium significantly prolonged the survival of heart allograft apparently by **inhibiting** antidonor antibodies in recipient rats.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effective suppression of brequinar sodium on accelerated allograft rejection in presensitized recipients)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 23 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 122:605 CA
TITLE: Blocking of heart allograft rejection by intercellular adhesion molecule-1 antisense oligonucleotides alone or in combination with other immunosuppressive modalities
AUTHOR(S): Stepkowski, Stanislaw M.; Tu, Yizheng; Condon, Thomas P.; Bennett, C. Frank
CORPORATE SOURCE: Department Surgery, University Texas Medical School, Houston, TX, 77030, USA
SOURCE: Journal of Immunology (1994), 153(11), 5336-46
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

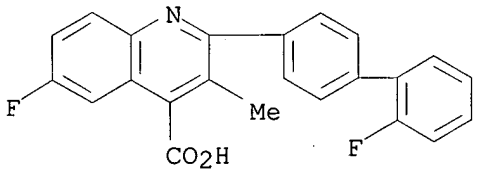
AB Intercellular adhesion mol.-1 (ICAM-1) binds circulating leukocytes through interactions with .beta.2 integrins, LFA-1, and macrophage Ag-1. The phosphorothioate antisense oligodeoxynucleotide, IP-3082, specific for ICAM-1 mRNA **inhibited** ICAM-1, but not vascular cell adhesion mol.-1, mRNA induction and expression of ICAM-1 mols. by mouse endothelioma cells. Scrambled control oligonucleotides were ineffective. Untreated C3H (H-2k) mice rejected C57BL/10 (H-2b) heart allografts with a mean survival time of 7.7 .+-. 1.4 days. Administration i.v. of IP-3082 by a 7-day osmotic pump prolonged the survival of heart allografts in a dose-dependent fashion: 1.25 mg/kg, to 11 .+-. 0 days; 2.5 mg/kg, to 12

.+-. 2.7 days; 5 mg/kg, to 14.1 .+-. 2.7 days; and 10 mg/kg, to 15.3 .+-. 5.8 days (all $p < 0.01$). Control IP-1082 (10 mg/kg) was ineffective (7 .+-. 0.8 days). Although 7-day anti-LFA-1 mAb (50 .mu.g/day; i.p.) prolonged allograft survival to 14.1 .+-. 2.7 days, the addn. of IP-3082 (5.0 mg/kg .times. 7 days) induced donor-specific transplantation tolerance (>150 days). Furthermore, IP-3082 (5 mg/kg .times. 7 days) acted synergistically with antilymphocyte serum, rapamycin, and brequinar, but not cyclosporin A: a single antilymphocyte serum (0.2 mL) i.p. injection alone prolonged graft survival to 10 .+-. 0.5 days ($p < 0.01$) and in combination with IP-3082 (5 mg/kg), to 32.2 .+-. 8.3 days ($p < 0.001$); rapamycin (0.1 mg/kg .times. 7 days; i.v.) alone prolonged survival to 13 .+-. 7.5 days ($p < 0.01$), and with IP-3082, to 32.4 .+-. 8.9 days ($p < 0.03$); brequinar (0.5 mg/kg .times. 7 days; oral gavage) alone to 12 .+-. 2.4 days ($p < 0.05$), and with IP-3082 (5 mg/kg), to 38.8 .+-. 30.2 days ($p < 0.01$); in contrast, cyclosporin A (5 mg/kg .times. 7 days; i.v.) alone produced graft survival of 9.8 .+-. 1.3 days ($p < 0.1$) and in combination with IP-3082 (5 mg/kg), produced survival of 7.8 .+-. 3.5 days (NS). Thus, antisense oligonucleotides may proffer a selective gene-targeted immunosuppressive therapy for organ transplantation.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blocking of heart allograft rejection by ICAM-1 antisense oligonucleotides alone or in combination with other immunosuppressive modalities)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 24 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 121:292245 CA

TITLE: Effect of brequinar sodium on accelerated cardiac allograft rejection in presensitized recipients

AUTHOR(S): Nozaki, S.; Ito, T.; Kamiike, W.; Uchikoshi, F.; Yamamoto, S.; Nakata, S.; Shirakura, R.; Miyata, M.; Matsuda, H.; et al.

CORPORATE SOURCE: 1st Department Surgery, Osaka University Medical School, Suita, 565, Japan

SOURCE: Transplantation Proceedings (1994), 26(4), 2333-5
CODEN: TRPPA8; ISSN: 0041-1345

DOCUMENT TYPE: Journal

LANGUAGE: English

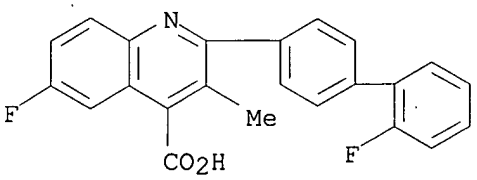
AB Brequinar (BQR)is effective in controlling accelerated rejection in presensitized recipients by **inhibiting** the humoral and cellular immune responses. When BQR therapy was stopped, the LEW rat recipients rejected BUF grafts in an acute fashion. Thus, it is essential to develop more effective strategies for controlling memorized B- and T-cell precursors.

IT **96187-53-0**, Brequinar
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(brequinar effect on accelerated cardiac allograft rejection in presensitized recipients)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 25 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 121:244979 CA

TITLE: Application of pharmacokinetically guided dose escalation with respect to cell cycle phase specificity

AUTHOR(S): Fuse, Eiichi; Kobayashi, Satoshi; Inaba, Makoto; Suzuki, Hiroshi; Sugiyama, Yuichi

CORPORATE SOURCE: Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., Sunto-Gun, 411, Japan

SOURCE: Journal of the National Cancer Institute (1994), 86(13), 989-96
CODEN: JNCIEQ; ISSN: 0027-8874

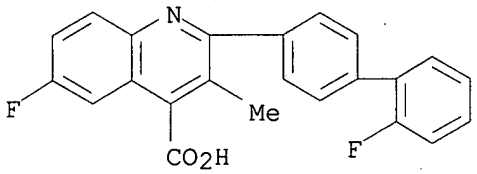
DOCUMENT TYPE: Journal

LANGUAGE: English

AB In 1986, the concept of pharmacokinetically guided dose escalation (PGDE) was proposed to predict the max. tolerated dose (MTD) of an antitumor drug in humans from animal data. We have previously shown that antitumor drugs can be classified into two types, depending on their cytotoxic mechanisms: type 1 drugs, which are cell cycle phase-nonspecific agents, i.e., area under the curve for drug concn. in the plasma vs. time (AUC)-dependent drugs; and type 2 drugs, which are cell cycle phase-specific agents, i.e., those that are time-dependent. The validity of the assumption that the AUC at the dose lethal for 10% of mice administered drug (LD10) is equal to the AUC at MTD for humans, the premise on which PGDE is based, was examd. for type 1 and 2 drugs. Findings in the literature, including those of Collins and coworkers, were retrospectively analyzed. The human/mouse ratios for the AUC were compared with each other and with the human/mouse dose ratios, based on milligram per m square of body surface area, the measurement currently used in clin. trials of antitumor drugs. For six of the type 1 drugs, the human/mouse ratio for the AUC of total drug (AUC) and that of unbound drug (AUCu), which has been considered a determinant of pharmacol. and toxicol. effects, were also compared. There was an excellent correlation between log AUC at LD10 for mice and log AUC at MTD for humans for type 1 drugs (r = .898), but not for type 2 drugs (r = .677). For type 1 drugs, the correlation between mouse AUC at LD10 and human AUC at MTD was better for unbound drug (r = .961) than for total drug (r = .892). The authors conclude that PGDE is useful for type 1 drugs; differences in protein binding between species should, however, be considered when using this method.

IT **96201-88-6**, Brequinar sodium
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(application of pharmacokinetically guided dose escalation for antitumor drugs with respect to cell cycle phase specificity)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



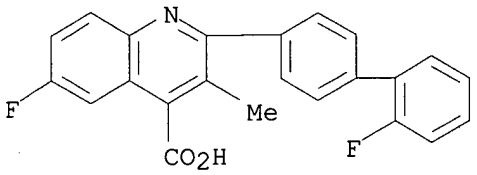
● Na

L20 ANSWER 26 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 121:169619 CA
TITLE: Relation between age and clearance rate of nine investigational anticancer drugs from phase I pharmacokinetic data
AUTHOR(S): Borkowski, Jane M.; Duerr, Mary; Donehower, Ross C.; Rowinsky, Eric K.; Chen, Tian-Ling; Ettinger, David S.; Grochow, Louise B.
CORPORATE SOURCE: Johns Hopkins Univ. Sch. Med., Baltimore, MD, 21287-8934, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1994), 33(6), 493-6
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aging influences the disposition and effects of several classes of drugs. Although drug clearance rate is correlated with toxicity for many anticancer drugs, few data have been published concerning the relationship of aging and clearance of chemotherapy. This study was performed to identify any relationship between age and clearance rate for anticancer drugs in phase I trials at the Johns Hopkins Oncol. Center. In a retrospective study, we examd. the clin. and pharmacokinetic data for 344 adults (aged 21-77 yr) who received 9 phase I drugs with linear clearance in 13 clin. trials. We sought correlations between age and clearance for each drug and for the whole group. Data available for 9 of the 13 trials were used to compare age (<65 or >65 yr) vs. dose delivered [< the max. tolerated dose (MTD) vs .gtoreq. the MTD] or toxicity (< grade 3 vs .gtoreq. grade 3). Of 344 patients, 81 (23.5%) were >65 yr old, 34 (9.9%) were .gtoreq.70 yr old, and 5 (1.5%) were .gtoreq.75 yr old. There was no significant correlation between drug clearance and age for individual drugs or the group as a whole. There was no significant difference between patients of the older and younger age groups with regard to dose or toxicity. Although only a small no. of patients aged .gtoreq.75 yr were treated, our results suggest that the elderly do not experience greater toxicity even when treated at doses comparable with those given younger patients and should not be excluded from phase I trials on the basis of age. As the population of the United States ages, more elderly patients will be candidates for chemotherapy. A more thorough examn. of the relationships between age, clearance rate, and toxicity can be accomplished as active drugs enter phase II/III studies.

IT **96187-53-0**, Brequinar
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (pharmacokinetics and toxicity of, age effect on, as anticancer drug in

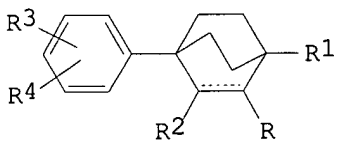
humans)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 27 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 121:133700 CA
TITLE: Preparation of [(bicycloctylphenyl)akoxy]akanoates and analogs as antiarthritics
INVENTOR(S): De, Nanteuil Guillaume; Vincent, Michel; Lila, Christine; Bonnet, Jacqueline; Fradin, Armel
PATENT ASSIGNEE(S): Adir et Cie., Fr.
SOURCE: Eur. Pat. Appl., 32 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 599732	A1	19940601	EP 1993-402850	19931124
EP 599732	B1	19970312		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
FR 2698355	A1	19940527	FR 1992-14058	19921124
FR 2698355	B1	19950120		
AU 9351856	A1	19940609	AU 1993-51856	19931122
AU 661210	B2	19950713		
JP 06228044	A2	19940816	JP 1993-292190	19931122
JP 2587902	B2	19970305		
CA 2109744	AA	19940525	CA 1993-2109744	19931123
US 5403953	A	19950404	US 1993-156299	19931123
ZA 9308792	A	19940630	ZA 1993-8792	19931124
AT 149997	E	19970315	AT 1993-402850	19931124
ES 2101269	T3	19970701	ES 1993-402850	19931124

PRIORITY APPLN. INFO.: FR 1992-14058 19921124
OTHER SOURCE(S): MARPAT 121:133700
GI



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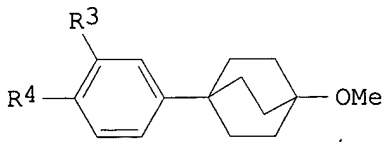


II

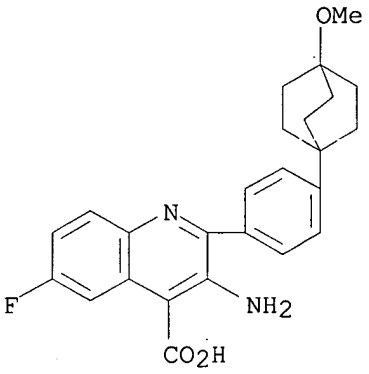
AB Title compds. [I; R = R2 = H when dashed line = bond; R,R2 = H, halo, OH, alkyl, alkoxy, etc. when dashed line = null; R1 = H, OH, (halo)alkyl, (halo)alkoxy, cyano, NH2, etc.; R3 = ZCO2H, CONHCH2CO2H, CH:CMeCO2H,

carboxybenzofuran-3-yl, etc.; R4 = H, halo, alkyl, alkoxy, etc.; Z = (O-interrupted)alkylene] were prepd. Thus, 3-MeC6H4CN was cyclocondensed with CH2:CHCO2Me to give 2-methoxycarbonyl-4-cyano-4-(3-methylphenyl)cyclohexanone which was converted in 5 steps to biccyclooctylbenzene II (R3 = CH2Br, R4 = H) which was condensed with HOCMe2CO2Et to give, after sapon., II (R3 = CH2OCMe2CO2Na, R4 = H). II (R3 = H, R4 = CH2OCMe2CO2Na) gave 100% **inhibition** of adjuvant-induced hypoalbuminemia at 100mg/kg/day orally in rats.

IT **157164-86-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antiarthritic)

RN 157164-86-8 CA

CN 4-Quinolinecarboxylic acid, 3-amino-6-fluoro-2-[4-(4-methoxybicyclo[2.2.2]oct-1-yl)phenyl]-, monosodium salt (9CI) (CA INDEX NAME)



L20 ANSWER 28 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 120:296580 CA

TITLE: Cytidine potentiates the **inhibitory** effect of brequinar sodium on xeno-MLR, antibody production, and concordant hamster to rat cardiac xenograft survival

AUTHOR(S): Woo, Jacky; Valdivia, Luis A.; Pan, Fan; Celli, Susanna; Fung, John J.; Thomson, Angus W.

CORPORATE SOURCE: Pittsburgh Transplant Inst., Pittsburgh, PA, 15213, USA

SOURCE: Annals of the New York Academy of Sciences (1993), 696(Immunosuppressive and Antiinflammatory Drugs), 227-34
CODEN: ANYAA9; ISSN: 0077-8923

DOCUMENT TYPE: Journal

LANGUAGE: English

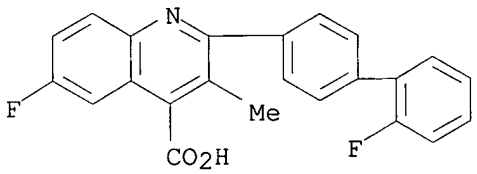
AB Strong proliferative responses of rat lymph node lymphocytes in response to irradiated hamster cells were obsd. in 5-day mixed lymphocyte cultures. Addn. of brequinar sodium (BQR) at the start of the culture period resulted in a dose-related **inhibition** of 3HTdR incorporation, with an IC50 of 1 .mu.g/mL; almost 90% **inhibition** of DNA synthesis was achieved with 5 .mu.g/mL BQR. Cytidine potentiated the **inhibitory** effect of BQR, but only at concns. of 0.5 .mu.g/mL BQR or above. When BQR and cytidine were added at the start of cultures, 90%

inhibition of the MLR was achieved with 1 .mu.g/mL BQR. Cytidine alone (0.1 mM) had no effect on the xeno MLR. The mean survival times of heterotropic hamster cardiac xenographs in the Lew rat was increased about 5 times when BQR and cytidine were administered. In vitro expts. also demonstrated that BQR alone or with cytidine was very effective in controlling IgM prodn. in IL-6-stimulated human SKW6,4 B cell lines. This effect may have contributed to the prolonged heart survival. Although BQR alone and BQR plus cytidine were both effect in controlling antihamster cytotoxic antibody prodn., no further redn. in antibodies by supplementation with cytidine was obsd. Thus, although the beneficial effect of combining BQR and cytidine in vivo is unclear, difficulties in interpretation of their effects may have arisen as a result of the rapid in vivo clearance rate of the drug and the stringency of the (xenograft) model employed.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(Ig formation and mixed lymphocyte reaction and heart transplant survival response to cytidine and)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 29 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 120:296259 CA

TITLE: Brequinar sodium, mycophenolic acid, and cyclosporin A **inhibit** different stages of IL-4- or IL-13-induced human IgG4 and IgE production in vitro

AUTHOR(S): Chang, Chia Chun J.; Aversa, Gregorio; Punnonen, Juha; Yssel, Hans; de Vries, Jan E.

CORPORATE SOURCE: Res. Inst. Mol. Cell. Biol., DNAX, Palo Alto, CA, 94304-1104, USA

SOURCE: Annals of the New York Academy of Sciences (1993), 696(Immunosuppressive and Antiinflammatory Drugs), 108-22
CODEN: ANYAA9; ISSN: 0077-8923

DOCUMENT TYPE: Journal

LANGUAGE: English

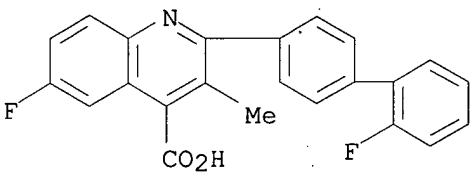
AB The authors investigated the effect of cyclosporin A (CsA), mycophenolic acid (MPA), and brequinar sodium (BQ) on human IgG4 and IgE synthesis induced by IL-4 or IL-13. BQ **inhibited** IL-4 and IL-13-induced IgG4 and IgE synthesis in cultures of peripheral blood mononuclear cells (PBMC) or highly purified B cells costimulated by anti-CD40 mAbs in a dose-dependent fashion. CsA and MPA had either suppressive or enhancing effects depending on the concns. tested. BQ **inhibited** IgG4 and IgE synthesis at concns. of 10-6-10-8 M, which did not affect T or B cell proliferation, indicating that the **inhibitory** effects of BQ on Ig prodn. were not directly related to **inhibition** of T or B cell

proliferation. In contrast, the **inhibitory** effects of MPA on Ig prodn. were directly assocd. with **inhibitory** effects on T and B cell proliferation. CsA blocked T and B cell proliferation at the same concn. (10-7 M) which enhanced IgG4 and IgE synthesis, indicating that redn. in T or B cell proliferation correlated with enhanced IgE prodn. CsA also **inhibited** CD40 ligand expression and IL-2, IL-4, IL-5, IFN-.gamma., and GM-CSF prodn. by activated CD4+ T cell clones, whereas MPA and BQ were ineffective, indicating that these compds. do not **inhibit** early events in T cell activation. The data indicate that BQ, MPA, and CsA block different stages of the IgG4 and IgE prodn. process. In addn., it was obsd. that CsA and MPA, in contrast to BQ, at lower concns. can also have potentiating effects on the prodn. of these Ig isotypes.

IT **96201-88-6**, Brequinar sodium
RL: PRP (Properties)
(interleukin 4 or 13-induced IgG4 and IgE formation **inhibition** by)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 30 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 120:208132 CA

TITLE: The prevention of accelerated cardiac allograft rejection in sensitized recipients after treatment with brequinar sodium

AUTHOR(S): Yasunaga, Chikao; Cramer, Donald V.; Chapman, Frances A.; Wang, Hong Kai; Barnett, Michelle; Wu, Guo Du; Makowka, Leonard

CORPORATE SOURCE: Cedars-Sinai Res. Inst., Cedars-Sinai Med. Cent., Los Angeles, CA, USA

SOURCE: Transplantation (1993), 56(4), 898-904
CODEN: TRPLAU; ISSN: 0041-1337

DOCUMENT TYPE: Journal

LANGUAGE: English

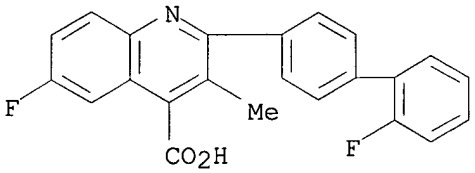
AB Brequinar sodium (BQR) is a novel immunosuppressive agent that is highly effective in preventing B lymphocyte-mediated antibody prodn. The authors have examd. the effects of BQR treatment in sensitized recipients on graft survival, donor-specific antibody responses (IgM and IgG), and the appearance of immunopathol. lesions present in the grafts. LEW rat recipients were sensitized with single ACI skin graft on day 7 and received heterotopic ACI cardiac grafts on day 0. The recipients rejected the cardiac grafts in an accelerated fashion at day 2.5 post-transplantation, compared to day 7.0 in unsensitized recipients. The animals were treated with low (3 mg/kg/day) or high (12 mg/kg/3x weekly) doses of BQR during skin graft sensitization and/or after challenge with ACI heart allografts. All groups treated with BQR showed significant

prolongation of graft survival in the sensitized recipients. The best survival was obsd. following high-dose BQR therapy during both sensitization and effector phases (median survival time = 40.0 days, P .mchlt. 0.001). Daily treatment with BQR (3 mg/kg/day) prevented IgM (but not IgG) antibody responses. Treatment with higher doses of BQR (12 mg/kg/3.times. weekly) before and after skin graft sensitization was effective in preventing both IgM and IgG prodn. In general, BQR treatment resulted in effective suppression of anti-donor antibody responses, stable graft function, and a redn. in the severity of the acute vascular lesions in the graft. The effectiveness of BQR in preventing accelerated graft rejection when used at 12 mg/kg/3.times. weekly was comparable to that seen with treatment of sensitized animals with CsA at 15 mg/kg/day for 30 days. Daily treatment with cyclophosphamide at 5 or 15 mg/kg/day was ineffective for preventing graft rejection in sensitized recipients. These results indicated that BQR may provide an important addn. to treatment protocols designed to prevent transplantation rejection in presensitized patients. BQR has the ability to significantly **inhibit** host cellular and humoral immune responses to the donor graft and this facet of the immunosuppressive activity of the drug may be responsible for preventing this aggressive form of rejection.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(heart allograft rejection prevention by)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 31 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 120:95764 CA
TITLE: Chemotherapeutic drug combinations
INVENTOR(S): Martin, Daniel S.; Stolfi, Robert L.; Colofiore, Joseph R.; Nord, L. D.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9323014	A1	19931125	WO 1993-US4775	19930520
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9343834	A1	19931213	AU 1993-43834	19930520
AU 684709	B2	19980108		
EP 641193	A1	19950308	EP 1993-914010	19930520
R: AT, BE, CH, DE, FR, GB, IE, IT, LI, NL				
JP 08506317	T2	19960709	JP 1993-503842	19930520

PRIORITY APPLN. INFO.: US 1992-885809 19920520

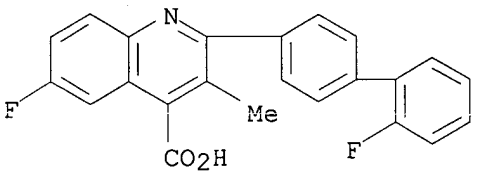
WO 1993-US4775 19930520

AB Drug combinations for the treatment of neoplastic diseases comprise (1) cellular energy depletion compns. contg. an **inhibitor** of purine nucleotide biosynthesis, a nicotinamide antagonist, and optionally an **inhibitor** of pyrimidine nucleotide biosynthesis and (2) apoptosis-inducing agents. For example, antineoplastic effects of combinations of N-(phosphonacetyl)-L-aspartic acid, 6-methylmercaptopurine riboside, 6-aminonicotinamide, and 5-fluorouracil in breast tumor-bearing mice were demonstrated.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(neoplasm treatment with purine nucleotide biosynthesis **inhibitors** and nicotinamide antagonists and)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 32 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 119:262136 CA

TITLE: Brequinar sodium **inhibits** interleukin-6-induced differentiation of a human B-cell line into IgM-secreting plasma cells

AUTHOR(S): Tamura, K.; Woo, J.; Bakri, M. T.; Thomson, A. W.

CORPORATE SOURCE: Med. Cent., Univ. Pittsburgh, Pittsburgh, PA, USA

SOURCE: Immunology (1993), 79(4), 587-93
CODEN: IMMUAM; ISSN: 0019-2805

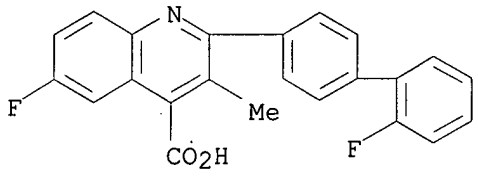
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Brequinar sodium (BQR) has been shown recently to be a potent immunosuppressive agent. This property has been attributed to the capacity of BQR to **inhibit** de novo pyrimidine nucleoside biosynthesis and consequently, to blockade the synthesis both of DNA and RNA. The influence of this new immunosuppressant on lymphocyte function has not been fully characterized. To det. the potential efficacy of BQR for the control of antibody-mediated graft rejection, which is of particular significance in the context of xenotransplantation, the authors have examd. the influence of the drug on interleukin-6-dependent IgM prodn. by the human B-cell line, SKW 6.4. At concns. up to 10 .mu.g/mL, BQR did not affect Con A-induced human peripheral blood lymphocyte proliferation or IL-6 prodn. by blood mononuclear leukocytes. In contrast, the drug was very effective in **inhibiting** IL-6-stimulated IgM prodn. by SKW 6.4 cells, with an optimal **inhibitory** concn. of 0.3 .mu.g/mL. As expected, addn. of exogenous uridine (0.1 mM), the precursor of uridine triphosphate (UTP), reversed the **inhibitory** effect of BQR on antibody prodn., while cytidine (0.1 mM) potentiated the **inhibitory** activity of the drug. It was further demonstrated that the **inhibition** of IgM prodn. was unrelated to DNA synthesis, indicating that BQR may affect IL-6 signal transduction and IgM prodn. in SKW 6.4 cells independent of any effect on cell proliferation.

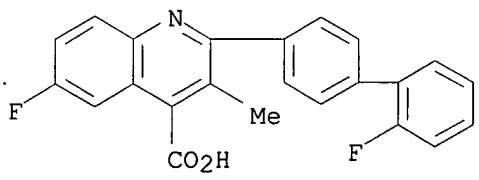
IT **96201-88-6**, Brequinar sodium

RL: BIOL (Biological study)
(**inhibition** of cytidine-induced human B-cell differentiation and IgM formation by, immunosuppression in relation to)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 33 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 119:216916 CA
TITLE: Comparative in vitro studies on the immunosuppressive effects of purine and pyrimidine synthesis **inhibitors**
AUTHOR(S): Zeevi, A.; Yao, G. Z.; Venkataramanan, R.; Duquesnoy, R. J.; Todo, S.; Fung, J. J.; Starzl, T. E.
CORPORATE SOURCE: Med. Cent., Univ. Pittsburgh, Pittsburgh, PA, USA
SOURCE: Transplantation Proceedings (1993), 25(1, Book 1), 781-3
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study demonstrates that brequinar sodium (BQR), mycopherolicacid (MPA), and mizorbine (MZR) **inhibit** the proliferative responses of normal T cells to mitogenic and allogeneic stimulation, whereas PALA has a minimal effect. The proliferative responses of T cells induced by T-cell receptor, IL-2, and protein kinase C are equally affected by BQR, MPA, and MZR, since these drugs block DNA synthesis. In contrast, FK 506 and CyA are more efficient in blocking signal transduction via T-cell receptors by **inhibiting** the transcription of early activation genes.
IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(T-cell proliferation **inhibition** by)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 34 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 119:131138 CA

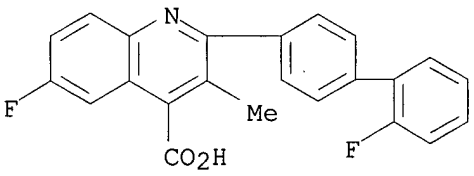
TITLE: Brequinar sodium effectively and potently suppresses allograft rejection in a heterotopic mouse heart transplant model
AUTHOR(S): Murphy, M. P.; Morris, R. E.
CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, USA
SOURCE: Transplantation Proceedings (1993), 25(3, Suppl. 2), 75-6
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present report extends the authors initial study of brequinar to include its (1) immunosuppressive potency in comparison with orally administered CsA, rapamycin, and FK 506; (2) schedule dependency; (3) ability to control advanced, first-set rejection; (4) ability to prevent accelerated rejection in presensitized recipients; and (5) immunosuppressive interaction with CsA.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(**inhibition** of rejection of heart allograft transplant by)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 35 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 119:131136 CA
TITLE: Mycophenolic acid and brequinar, **inhibitors** of purine and pyrimidine synthesis, block the glycosylation of adhesion molecules
AUTHOR(S): Allison, A. C.; Kowalski, W. J.; Muller, C. J.; Waters, R. V.; Eugui, E. M.
CORPORATE SOURCE: Syntex Discovery Res., Palo Alto, CA, USA
SOURCE: Transplantation Proceedings (1993), 25(3, Suppl. 2), 67-70
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English

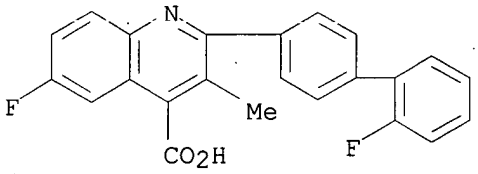
AB A great deal of research is being done on the potential clin. utility of antibodies against adhesion mols., as well as administering recombinant adhesion mols. themselves, or oligosaccharides that bind adhesion mols. The authors propose an alternative strategy which is attainable with drugs that have already shown efficacy and safety in humans. The authors' strategy is to **inhibit** the glycosylation of adhesion mols. by depleting pools of GTP and UTP which are required for this biochem. reaction. Mycophenolic acid (MPA) depletes GTP which is required for the formation of GDP-fucose and GDP-mannose, intermediates in the transfer of fucose and mannose to dolichol phosphate-linked oligosaccharides and then to proteins. Brequinar (BQR) depletes UTP, which is required for the

formation of UDP derivs. of glucose, galactose, and the corresponding amines. Transfer of one of these, UDP-GlcNac, to dolichol phosphate is the first step in glycosylation. Because MPA depletes GTP and BQR depletes UTP more effectively in lymphocytes than in other cell types, **inhibition** of glycosylation by these drugs will be greater in lymphocytes. Hence, **inhibition** of the interactions of lymphocytes with endothelial cells and other cell types can be achieved with doses of MPA (or the prodrug mycophenolate mofetil) or of BQR that do not produce nephrotoxicity, hepatotoxicity, or other serious side effects. Moreover, because BQR and MPA **inhibit** sequential steps in glycosylation, the two drugs used together would be expected to have greater effects than either one alone.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(glycosylation adhesion mols. **inhibition** by mycophenolic acid and)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 36 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 119:131135 CA

TITLE: Cardiac graft rejection in hypersensitized recipients: prevention of antibody response and graft rejection using brequinar sodium

AUTHOR(S): Yasunaga, C.; Cramer, D. V.; Chapman, F. A.; Wang, H. K.; Barnett, M.; Wu, G. D.; Makowka, L.

CORPORATE SOURCE: Cedars-Sinai Res. Inst., Cedars-Sinai Med. Cent., Los Angeles, CA, USA

SOURCE: Transplantation Proceedings (1993), 25(3, Suppl. 2), 65-6
CODEN: TRPPA8; ISSN: 0041-1345

DOCUMENT TYPE: Journal

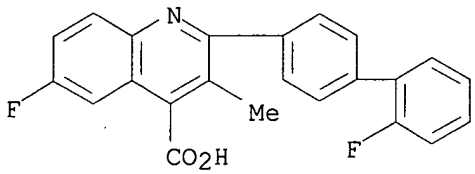
LANGUAGE: English

AB In the present expts., the authors demonstrate that the immunosuppressive activity of BQR is effective in preventing accelerated graft rejection of ACI rat heart grafts transplanted to presensitized LEW rat recipients, and this prolongation of survival is assocd. with suppression of recipient antidonor antibody response.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(heart graft rejection prevention by, in hypersensitized recipients, antibody response **inhibition** in)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)

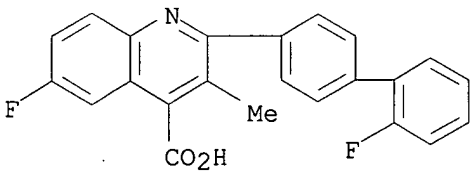


● Na

L20 ANSWER 37 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 119:131132 CA
TITLE: Evaluation of the use of brequinar sodium and cyclosporine combination therapy for preventing rat cardiac allograft rejection
AUTHOR(S): Cosenza, C. A.; Cramer, D. V.; Eiras-Hreha, G.; Cajulis, E.; Wang, H. K.; Makowka, L.
CORPORATE SOURCE: Cedars-Sinai Res. Inst., Cedars-Sinai Med. Cent., Los Angeles, CA, USA
SOURCE: Transplantation Proceedings (1993), 25(3, Suppl. 2), 57-8
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The use of subtherapeutic doses of BQR and CsA in combination represents an effective treatment for prolonging heterotopic cardiac allograft survival in rodents. Effective treatment to prolong allograft survival is assocd. with plasma drug levels that **inhibited** mitogen-induced lymphocyte proliferation, particularly in animals treated simultaneously with both drugs. This data supports the potential for the future use of BQR as part of a polytherapeutic immunosuppressive regimen for preventing solid organ rejection.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(cyclosporine and, in prevention of heart allograft rejection)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

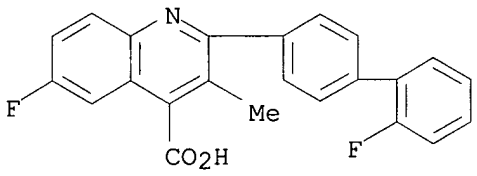
L20 ANSWER 38 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 119:130726 CA
TITLE: Prevention of vascularized allograft and xenograft rejection in rodents by brequinar sodium

AUTHOR(S): Cramer, D. V.; Chapman, F. A.; Makowka, L.
CORPORATE SOURCE: Cedars-Sinai Res. Inst., Cedars-Sinai Med. Cent., Los Angeles, CA, USA
SOURCE: Transplantation Proceedings (1993), 25(3, Suppl. 2), 23-8
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 28 refs. The data that has been obtained from preclin. studies in rodents demonstrate that BQR is an effective primary immunosuppressive agent with important advantages for use in transplantation immunotherapy. The drug is highly effective when used as a single agent to prevent the rejection of a variety of vascularized allografts and xenografts. BQR is easily administered orally, the drug displays a high level of bioavailability, and drug plasma levels and immunosuppressive activity can be directly measured. The adverse effects seen with the drug are those normally assocd. with antiproliferative drugs and are predictable and easily reversed by treatment withdrawal. Most importantly, perhaps, is the broad range of synergistic activity when used in combination with new immunosuppressive drugs. The authors believe that the combination of these attributes sep. BQR from many of the new drugs now under study.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(allograft and xenograft rejection **inhibition** by)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 39 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 119:108586 CA
TITLE: The synergistic interactions in vitro and in vivo of brequinar sodium with cyclosporine or rapamycin alone and in triple combination
AUTHOR(S): Kahan, Barry D.; Tejpal, Neelam; Gibbons-Stubbers, Sheena; Tu, Yizheng; Wang, Mouer; Stepkowski, Stanislaw; Chou, Ting Chao
CORPORATE SOURCE: Med. Sch., Univ. Texas, Houston, TX, 77030, USA
SOURCE: Transplantation (1993), 55(4), 894-900
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English

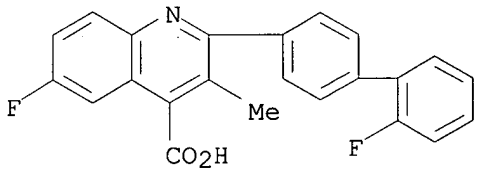
AB The rigorous median-effect anal. was used to assess the interactions between cyclosporine and drugs that **inhibit** nucleotide synthesis pathways. Using in vitro proliferation assays wherein human lymphocytes were triggered by phytohemagglutinin, anti-CD3 monoclonal antibody, or mixed lymphocyte reactions, CsA was shown to display additive interactions

with 6-mercaptopurine (6-MP), mizoribine (MZB), and mycophenolic acid (MPA), and a synergistic interaction with brequinar (BQR). In the in vitro assays, BQR contributed a further synergistic effect to the double-drug combination CsA/rapamycin (RAPA). Of the four **inhibitors** of nucleotide synthesis pathways, only BQR noncompetitively **inhibited** IL-2-stimulated proliferation of the CTLL-2 cell line. Using the in vivo assay of heterotopic Buffalo (BUF, RT-1b) cardiac allografts in Wistar-Furth (WFu, RT-1u) hosts, oral administration of BQR displayed about 100% bioavailability, which, like the bolus i.v. mode, was eight-fold more effective than continuous i.v. infusions. Furthermore, median-effect anal. of serial amts. of orally administered BQR demonstrated that it contributes synergistically to the immunosuppressive effects of i.v. delivered CsA/RAPA (0.5/0.01 mg/kg/day). The degree of synergism was proportionate to the extent of the immunosuppression. These findings document the potency of the Cs/RAPA/BQR triple-drug combination and suggest that the synergistic effects may permit dose redns. of each component, thereby mitigating toxicities resulting from the large amts. of individual agents necessary to achieve allo-unresponsiveness.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(immunosuppression by, cyclosporine and rapamycin synergistic interaction with)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 40 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 119:85645 CA

TITLE: Hamster-to-rat heart and liver xenotransplantation with FK506 plus antiproliferative drugs

AUTHOR(S): Murase, Noriko; Starzl, Thomas E.; Demetris, Anthony J.; Valdivia, Luis; Tanabe, Minoru; Cramer, Donald; Makowka, Leonard

CORPORATE SOURCE: Health Sci. Cent., Univ. Pittsburgh, Pittsburgh, PA, 15213, USA

SOURCE: Transplantation (1993), 55(4), 701-8
CODEN: TRPLAU; ISSN: 0041-1337

DOCUMENT TYPE: Journal

LANGUAGE: English

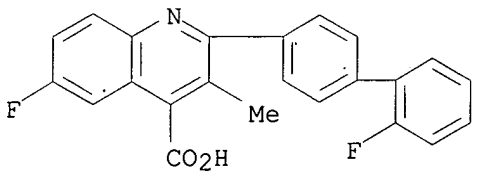
AB Heterotopic hamster hearts transplanted to unmodified LEW rats underwent humoral rejection in 3 days. Survival was prolonged to a median of 4 days with 2 mg/kg/day FK506. As monotherapy, 15 mg/kg/day cyclophosphamide greatly prolonged graft survival-far more than could be accomplished with RS-61443, brequinar (BQR), mizoribine, methotrexate, or deoxyspergualin. However, when FK506 treatment, which was ineffective alone, was combined with a short induction course (14 or 30 days) of subtherapeutic BQR,

RS-61443, or cyclophosphamide, routine survival of heart xenografts was possible for as long as the daily FK506 was continued. In addn., a single large dose of 80 mg/kg cyclophosphamide 10 days preoperatively allowed routine cardiac xenograft survival under FK506. The ability of these antimetabolites to unmask the therapeutic potential of FK506 correlated, although imperfectly, with the prevention of rises of preformed heterospecific cytotoxic antibodies immediately postoperatively. As an adjunct to FK506, azathioprine was of marginal value, whereas mizoribine, methotrexate, and deoxyspergualin (DSPG) were of intermediate efficacy. After orthotopic hepatic xenotransplantation, the perioperative survival of the liver with its well-known resistance to antibodies was less dependent than the heart on the antimetabolite component of the combined drug therapy, but the unsatisfactory results with monotherapy of FK506, BQR, RS-61443, or cyclophosphamide were changed to routine success by combining continuous FK506 with a short course of any of the other drugs. Thus, by breaking down the antibody barrier to xenotransplantation with these so-called antiproliferative drugs, it has been possible with FK506 to transplant heart and liver xenografts with consistent long-term survival of healthy recipients.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(heart and liver xenotransplant survival increase by FK506 and)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 41 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 118:73321 CA

TITLE: Cytokine gene expression in murine lymphocytes activated in the presence of FK 506, bredinin, mycophenolic acid, or brequinar sodium

AUTHOR(S): Lemster, B.; Woo, J.; Strednak, J.; Wang, S. C.; Todo, S.; Starzl, T. E.; Thomson, A. W.

CORPORATE SOURCE: Dep. Surg., Univ. Pittsburgh, Pittsburgh, PA, 15213, USA

SOURCE: Transplantation Proceedings (1992), 24(6), 2845-6
CODEN: TRPPA8; ISSN: 0041-1345

DOCUMENT TYPE: Journal

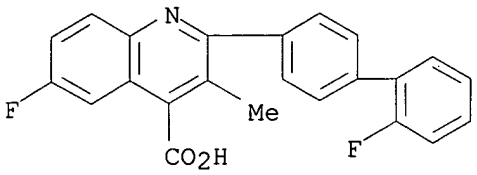
LANGUAGE: English

AB FK 506 **inhibited** expression of the gene for interleukin 2, but not that of the gene for interleukin 10, in activated mouse lymphocytes. The other title immunosuppressants either had no effect (mycophenolic acid and bredinin) or nonselectively reduced the expression of all genes studied, including constitutive genes (brequinar Na).

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(genes for interleukins 2 and 10 response to)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



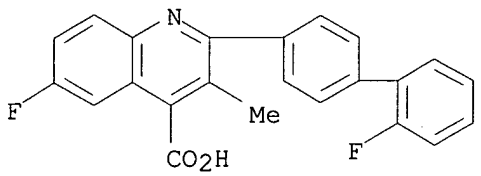
● Na

L20 ANSWER 42 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 118:362 CA
TITLE: Biochemical modulation of 5-fluorouracil with or without leucovorin by a low dose of brequinar in MGH-U1 cells
AUTHOR(S): Chen, Tian Ling; Erlichman, Charles
CORPORATE SOURCE: Dep. Pharmacol. Med., Univ. Toronto, Toronto, ON, M4X 1K9, Can.
SOURCE: Cancer Chemotherapy and Pharmacology (1992), 30(5), 370-6
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Combination of low doses of de novo pyrimidine biosynthesis **inhibitors** with 5-fluorouracil (FU) has been proposed to increase the antitumor activity of FU. Brequinar is such an **inhibitor** that has little clin. antitumor effect when used alone. The authors detd. the clonogenic survival of MGH-U1 cells treated with FU .+-. leucovorin (LV) .+-. brequinar and examd. the effects of these treatments on thymidylate synthase (TS). After 24 h exposure, the concns. resulting in 50% **inhibition** of cell growth (IC50) for brequinar, FU, and FU + LV (100 .mu.M) were 0.4, 20, and 10 .mu.M, resp. Both 24 h pretreatment and 48 h continuous treatment with the IC10 (0.1 .mu.M) of brequinar increased the cytotoxicity of FU but did not enhance that of FU + LV. Simultaneous 24 h exposure to 0.1 .mu.M brequinar and FU .+-. LV did not increase the cytotoxicity of FU .+-. LV. Intracellular cytidine triphosphate (CTP) and uridine triphosphate (UTP) pools, free TS binding sites, and levels of free fluorodeoxyuridine monophosphate (FdUMP) and deoxyuridine monophosphate (dUMP) were measured in cells pretreated with 0.1 .mu.M brequinar for 24 h alone or followed by a 2-h exposure to FU (25 .mu.M) + LV (100 .mu.M). In brequinar-treated cells, CTP and UTP pools amounted to 68% and 46% of control values, resp. The free TS binding sites remaining amounted to 70% of control values in cells treated with FU and 9% of control levels in those treated with FU + brequinar. Free FdUMP levels increased 5-fold in cells pretreated with brequinar as compared with those treated with FU alone. The increased formation of FdUMP was **inhibited** by simultaneous exposure to 100 .mu.M hypoxanthine and 25 .mu.M FU. Intracellular dUMP levels were not affected by brequinar. Thus, a low dose of brequinar increases the cytotoxicity of FU but does not enhance that of FU + LV when exposure to brequinar precedes FU treatment. This potentiation appears to be mediated by the increased formation of FdUMP as a consequence of an increase in the cosubstrate phosphoribosyl pyrophosphate (PRPP).

IT **96187-53-0**
RL: BIOL (Biological study)
(neoplasm **inhibition** by fluorouracil and leucovorin and, in human cells, mechanism of)

RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)

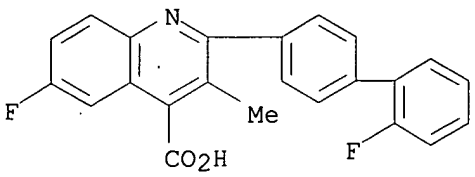


L20 ANSWER 43 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 118:134 CA
TITLE: Phase II perclinical drug screening in human tumor xenografts: a first European multicenter collaborative study
AUTHOR(S): Boven, Epie; Winograd, Benjamin; Berger, Dietmar P.; Dumont, M. Patrick; Braakhuis, Boudewijn J. M.; Fodstad, Oystein; Langdon, Simon; Fiebig, Heiner H.
CORPORATE SOURCE: Dep. Med. Oncol., Free Univ. Hosp., Amsterdam, Neth.
SOURCE: Cancer Research (1992), 52(21), 5940-7
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In a European joint project carried out in 6 labs., a disease-oriented program was set up consisting of a panel of 7 tumor types, each represented by 4 to 8 different human tumor lines, for secondary screening of promising anticancer drugs. Human tumor lines were selected on the basis of differences in histol., growth rate, and sensitivity to conventional cytostatic agents. Xenografts were grown s.c. in nude mice, and treatment was started when tumors reached a mean diam. of 6 mm in groups of mice where at least 6 tumors were evaluable. Drugs were given at the max. tolerated dose. For evaluation of drug efficacy, median tumor growth curves were drawn, and specific growth delay and treated/control .times. 100% were calcd. Doxorubicin (8 mg/kg i.v. days 1 and 8) was effective (treated/control <50%, and specific growth delay >1.0) in 0 of 2 breast cancers, 1 of 3 colorectal cancers, 2 of 5 head and neck cancers, 3 of 6 non-small cell lung cancers, 4 of 6 small cell lung cancers, 0 of 3 melanomas, and 3 of 6 ovarian cancer lines. Amsacrine (8 mg/kg i.v. days 1 and 8) was not effective, while datelliptium (35 mg/kg i.p. days 1 and 8) was active against 2 of 6 small cell lung cancer lines. Brequinar sodium (50 mg/kg i.p. days 1-5) showed efficacy in 4 of 5 head and neck cancers, 5 of 8 non-small cell lung cancers, and 4 of 5 small cell lung cancer lines. The project has been shown to be a feasible approach. Clin. activity for doxorubicin and inactivity for amsacrine against solid tumor types was confirmed in the human tumor xenograft panel. Addnl. anticancer drugs will be studied in the European joint project to further define the reliability of this novel, promising screening approach.

IT **96201-88-6**, Brequinar sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of, in phase II preclin. screening, in human tumor xenografts, in European multicenter study)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)

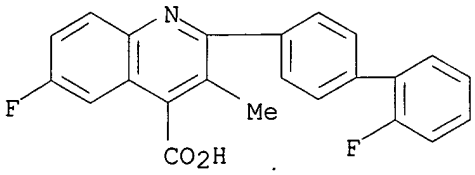


● Na

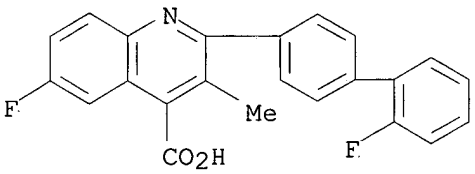
L20 ANSWER 44 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 117:245196 CA
TITLE: The prolongation of concordant hamster-to-rat cardiac xenografts by brequinar sodium
AUTHOR(S): Cramer, Donald V.; Chapman, Frances A.; Jaffee, Bruce D.; Zajac, Ihor; Hreha-Eiras, Gabriella; Yasunaga, Chikao; Wu, Guo Du; Makowka, Leonard
CORPORATE SOURCE: Dep. Surg., Cedars-Sinai Med. Cent., Los Angeles, CA, 90211, USA
SOURCE: Transplantation (1992), 54(3), 403-8
CODEN: TRPLAU; ISSN: 0041-1337
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Brequinar sodium (BQR) prevents cell proliferation by virtue of its **inhibition** of de novo pyrimidine biosynthesis. The immunosuppressive activity of BQR is highly effective in prolonging heart, liver, and kidney allograft survival in the rat. In these expts., we have tested the ability of BQR to prevent the rejection of concordant cardiac xenografts. LEW inbred rats transplanted with heterotopic hamster hearts were treated orally with brequinar sodium as a single agent. The survival of the cardiac xenografts was significantly prolonged with a variety of treatment regimens. The most effective treatment was the daily oral administration of BQR at 3 mg/kg. At this level, the median graft survival was approx. 25 days. Four animals had hamster heart xenografts that functioned for more than 90 days. The prolonged survival of the xenografts was assocd. with relatively const. plasma drug levels of approx. 1 to 3 .mu.g/mL and a marked suppression of IgM prodn. At rejection, there was a significant rise in IgM levels compared with those of recipients with stable xenografts. In vitro MLR responses were effectively **inhibited** by BQR, with an IC50 of 0.08 .mu.g/mL. The results of these expts. demonstrate that BQR is a new immunosuppressive agent that is highly effective as a single agent in prolonging the survival of hamster-to-rat cardiac xenografts. The prolonged xenograft survival is assocd. with effective suppression of rat antihamster antibody prodn., suggesting that brequinar sodium may be an important addn. to multidrug immunosuppressive regimes designed to prevent B and T lymphocyte-mediated immune responses.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(prolongation of concordant hamster-to-rat cardiac xenografts by)
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 45 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 117:204335 CA
TITLE: Preclinical studies with brequinar sodium: a novel anticancer agent
AUTHOR(S): Chen, Shih Fong; Dexter, Daniel L.
CORPORATE SOURCE: Glenolden Lab., E.I. Dupont de Nemours and Co., Glenolden, PA, 19036, USA
SOURCE: Developments in Oncology (1992), 68(Cytotoxic Anticancer Drugs: Models Concepts Drug Discovery Dev.), 261-80
CODEN: DEOND5; ISSN: 0167-4927
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 29 refs.
IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(preclin. pharmacol. of, as antitumor agent)
RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

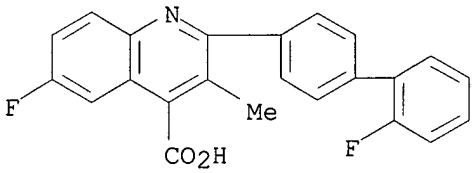
L20 ANSWER 46 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 117:62549 CA
TITLE: Therapy of chronic relapsing experimental allergic encephalomyelitis and the role of the blood-brain barrier: elucidation by the action of Brequinar sodium
AUTHOR(S): O'Neill, J. K.; Baker, D.; Davison, A. N.; Maggon, K. K.; Jaffee, B. D.; Turk, J. L.
CORPORATE SOURCE: Dep. Pathol., R. Coll. Surg. England, London, UK
SOURCE: Journal of Neuroimmunology (1992), 38(1-2), 53-62
CODEN: JNRIDW; ISSN: 0165-5728
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The immunosuppressive effect of the novel 4-quinoline carboxylic acid deriv. Brequinar sodium on the chronic relapsing exptl. allergic encephalomyelitis CREAE model in the Biozzi AB/H mouse was investigated.

Although Brequinar sodium actively **inhibited** peripheral immune responses, it showed a limited potential to control an ongoing disease of the central nervous system (CNS). Doses of 25 mg/kg **inhibited** in vivo induced proliferative response and prevented EAE when treated from day 9 post-inoculation (p.i.). However, when administered from day 12 p.i. or during the post-acute remission phase-limited effects on the course of disease were obsd. By comparison, treatment with a single high dose of cyclophosphamide (200 mg/kg) at these time points was significantly effective in controlling disease. As a possible explanation of the obsd. results it is suggested that for a compd. to be effective in treating an ongoing immune response in the CNS, it must be capable of crossing the blood-brain barrier and act on the disease-inducing cells activated within the CNS. This hypothesis is supported by the finding that intracerebral injections of Brequinar sodium on day 12 p.i. significantly **inhibited** disease progression. This suggests that strategies aimed at controlling immune-mediated disease of the CNS require therapeutic doses of the compds. to be delivered into the CNS.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(chronic relapsing exptl. allergic encephalomyelitis therapy with, blood-brain barrier permeability in, multiple sclerosis in relation to)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 47 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 116:207500 CA

TITLE: The effect of a new immunosuppressive drug, brequinar sodium, on heart, liver, and kidney allograft rejection in the rat

AUTHOR(S): Cramer, Donald V.; Chapman, Frances A.; Jaffee, Bruce D.; Jones, Elizabeth A.; Knoop, Michael; Hreha-Eiras, Gabriella; Makowka, Leonard

CORPORATE SOURCE: Dep. Surg., Cedars-Sinai Med. Cent., Los Angeles, CA, 90211, USA

SOURCE: Transplantation (1992), 53(2), 303-8
CODEN: TRPLAU; ISSN: 0041-1337

DOCUMENT TYPE: Journal

LANGUAGE: English

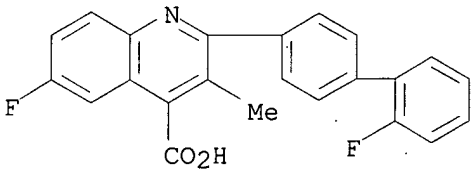
AB The efficacy of BQR in preventing allograft rejection was evaluated utilizing exptl. models of heterotopic heart and kidney and orthotopic liver transplantation in an MHC and non-MHC mismatched ACI.fwdarw.LEW rat strain combination. The immunosuppressive activity of BQR is illustrated by its ability to **inhibit** the development of delayed-type hypersensitivity to DNFB in mice. When BQR was administered orally throughout the sensitization and elicitation phases of the DNFB contact sensitivity response, it was found to be a potent immunosuppressant with an ED50 value of 0.5 mg/kg. This immunosuppressive activity is also seen in vitro, where BQR is capable of **inhibiting** the mixed lymphocyte response between allogeneic ACI and LEW rat strains with an IC50 of 150 ng/mL. The immunosuppressive activity of BQR is highly

effective in prolonging heart, liver, and kidney allograft survival in the rat. Cardiac allografts are not rejected during the period of drug treatment at dosage levels of 12 to 24 mg/kg orally three times weekly. The grafts survive until the drug is discontinued (30 days posttransplantation), and the grafts are then rejected approx. 14 days later. Liver and kidney allografts are permanently accepted by approx. 50 to 90% of the recipient rats following 30 days of treatment with BQR at 12 mg/kg. The tolerance that is induced to the liver grafts extends in the majority of animals to greater than 250 days and is specific for the donor ACI strain. Challenge of long-term liver graft survivors with donor cardiac grafts is assocd. with permanent survival of donor, but not third-party, heart grafts. Combination therapy consisting of suboptimal doses of BQR and CsA demonstrates that the combination of these two immunosupprssive drugs results in an increased efficacy in prolonging graft survival. The results of these allograft expts. demonstrate that this new immunosuppressive agent is highly effective in preventing allograft rejection in the rat. The antiproliferative activity of BQR is effective for **inhibiting** T-lymphocyte-mediated immune responses, and Brequinar sodium should be an important addn. to a polytherapeutic approach in the treatment of organ graft rejection.

IT **96201-88-6**, Brequinar sodium
RL: BIOL (Biological study)
(allograft rejection **inhibition** by, in heart and liver and kidney)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 48 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 116:143852 CA

TITLE: Treatment of organ transplantation rejection with immunosuppressants

INVENTOR(S): Ackerman, Neil Richard; Jaffee, Bruce Donald

PATENT ASSIGNEE(S): Du Pont Merck Pharmaceutical Co., USA

SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9119498	A1	19911226	WO 1991-US3788	19910605
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
US 5204329	A	19930420	US 1990-535672	19900611

AU 9180873	A1	19920107	AU 1991-80873	19910605
AU 664354	B2	19951116		
EP 537191	A1	19930421	EP 1991-910880	19910605
EP 537191	B1	19980429		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05507697	T2	19931104	JP 1991-510655	19910605
AT 165511	E	19980515	AT 1991-910880	19910605
ES 2114888	T3	19980616	ES 1991-910880	19910605
IL 98425	A1	19950629	IL 1991-98425	19910610
ZA 9104456	A	19930224	ZA 1991-4456	19910611
PRIORITY APPLN. INFO.:			US 1990-535672	19900611
			WO 1991-US3788	19910605

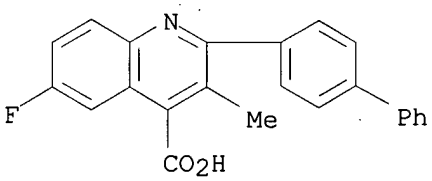
OTHER SOURCE(S): MARPAT 116:143852

AB 2-Phenyl-4-quinolinecarboxylic acid derivs., such as 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinolinecarboxylic acid (I), in combination with other immunosuppressive agents are useful for the treatment and prevention of transplantation rejection, graft vs. host disease, autoimmune diseases, and chronic inflammatory diseases. The 2-phenyl-4-quinolinecarboxylic acid derivs. have a unique mechanism of action compared to other known immunosuppressive agents, and therefore have not been assocd. with the nephrotoxicity and hepatoxicity seen with other immunosuppressants. In addn., the combination of drugs has a synergistic effect. I was tested in combination with cyclosporin A or azathioprine for the **inhibition** of the contact sensitivity response to 2,4-dinitrofluorobenzene in mice.

IT **96187-27-8D**, mixts. with immunosuppressant
RL: BIOL (Biological study)
(organ transplantation rejection and chronic inflammation treatment with)

RN 96187-27-8 CA

CN 4-Quinolinecarboxylic acid, 2-[1,1'-biphenyl]-4-yl-6-fluoro-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 49 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 116:99301 CA

TITLE: Maleic anhydride copolymers as antidotes for the cytotoxicity of neoplasm **inhibitors**

INVENTOR(S): Bach, Ardalan; Shanahan, William R., Jr.

PATENT ASSIGNEE(S): Searle, G. D., and Co., USA

SOURCE: Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

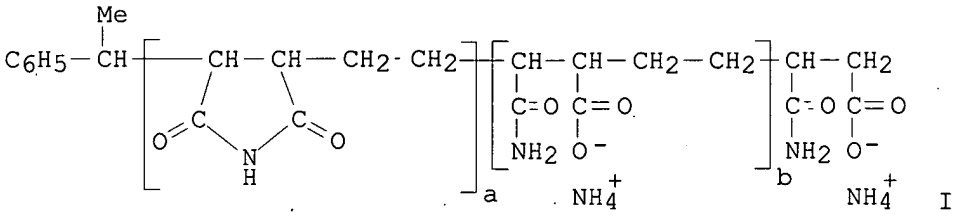
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 393575	A1	19901024	EP 1990-107246	19900417
EP 393575	B1	19940316		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				

CA 2014732	AA	19901017	CA 1990-2014732	19900417
JP 02292227	A2	19901203	JP 1990-101530	19900417
AT 102838	E	19940415	AT 1990-107246	19900417
ES 2062155	T3	19941216	ES 1990-107246	19900417
PRIORITY APPLN. INFO.:			US 1989-339503	19890417
			EP 1990-107246	19900417

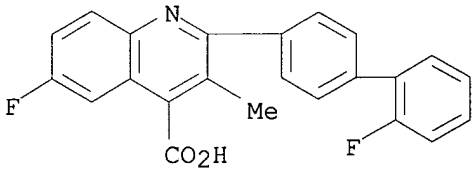
OTHER SOURCE(S): MARPAT 116:99301
GI



AB Half-amide:half-imide copolymers comprising ethylene and maleic anhydride moieties (structure given), specifically carbetimer (I; a/b = 1:2-5), decrease the cytotoxic side effects of neoplasm **inhibitors**. Mice treated i.v. with 21 mg adriamycin/kg died within 5 days. When 1700 mg I/kg was administered concomitantly, no lethality was shown for >30 days.

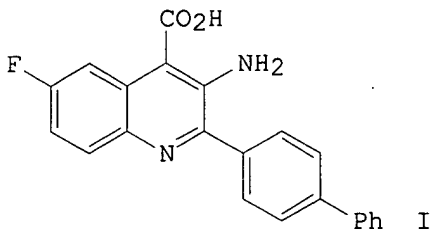
IT **96201-88-6**, Brequinar sodium
RL: PRP (Properties)
(cytotoxicity of, maleic anhydride copolymer antidote for)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



L20 ANSWER 50 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 115:174270 CA
TITLE: Antiinflammatory and antiarthritic properties of a substituted quinoline carboxylic acid: CL 306,293
AUTHOR(S): Sloboda, Adolph E.; Powell, Dennis; Poletto, John F.; Pickett, Walter C.; Gibbons, James J., Jr.; Bell, Duncan H.; Oronsky, Arnold L.; Serwar, Suresh S.
CORPORATE SOURCE: Med. Res. Div., American Cyanamid Co., Pearl River, NY, 10965, USA
SOURCE: Journal of Rheumatology (1991), 18(6), 855-60
CODEN: JRHUA9; ISSN: 0315-162X
DOCUMENT TYPE: Journal
LANGUAGE: English

GI

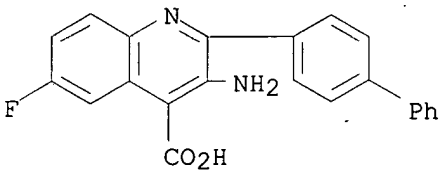


AB CL 306,293 (I), a substituted quinoline carboxylic acid at a daily oral dose between 1.5 and 3.0 mg/kg suppressed the inflammation and joint destruction (radiol. criteria) assocd. with both developing and established adjuvant arthritis. When a weekly oral dosing regimen was used, joint destruction was attenuated when this agent was administered at a dose of 50 to 200 mg/kg. Inflammation assocd. with a delayed type hypersensitivity reaction in dogs was suppressed at a daily oral dose of 0.25 mg/kg or a weekly dose of 1 mg/kg. At efficacious doses, CL 306,293 had no effects on cyclooxygenase or lipoxygenase activities nor did it have an effect on carrageenin induced paw edema. In acute tests, the compd. was not ulcerogenic. The above observations indicate that the antiinflammatory effects of CL 306,293 are distinct from those obsd. with nonsteroidal antiinflammatory agents. Mechanistic studies described elsewhere indicate that CL 306,293 down regulates T cell function and this mechanism may account, at least in part, for the antiinflammatory and antiarthritic properties obsd. in animal models of inflammation and joint destruction.

IT **131745-25-0**, CL 306293
RL: BIOL (Biological study)
(antiinflammatory and antiarthritic, mechanism of action of)

RN 131745-25-0 CA

CN 4-Quinolinecarboxylic acid, 3-amino-2-[1,1'-biphenyl]-4-yl-6-fluoro- (9CI) (CA INDEX NAME)



L20 ANSWER 51 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 114:61948 CA

TITLE: Preparation of quinolinecarboxylic acids as antiarthritic agents

INVENTOR(S): Poletto, John Frank; Powell, Dennis William; Boschelli, Diane Harris

PATENT ASSIGNEE(S): American Cyanamid Co., USA

SOURCE: Eur. Pat. Appl., 42 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

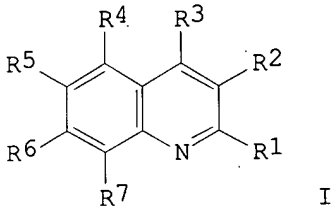
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 379145	A2	19900725	EP 1990-100839	19900116
EP 379145	A3	19910717		
EP 379145	B1	19970507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE				
US 4968702	A	19901106	US 1989-298585	19890117
IL 92898	A1	19941128	IL 1989-92898	19891227
CA 2007740	AA	19900717	CA 1990-2007740	19900115
AU 9048502	A1	19900726	AU 1990-48502	19900116
AU 624471	B2	19920611		
JP 02229166	A2	19900911	JP 1990-4637	19900116
JP 3004025	B2	20000131		
ZA 9000299	A	19901031	ZA 1990-299	19900116
AT 152711	E	19970515	AT 1990-100839	19900116
ES 2100851	T3	19970701	ES 1990-100839	19900116

PRIORITY APPLN. INFO.: US 1989-298585 A 19890117
OTHER SOURCE(S): MARPAT 114:61948
GI

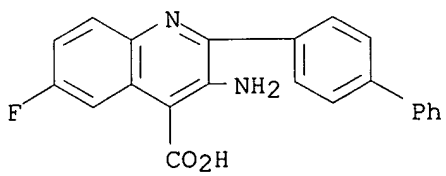


I

AB The compds. I (R1 = substituted Ph, PhO, PhS, PhSO, PhSO2; R2 = (substituted) NH2; R3 = HO2C, NCCH2O2C, H2NNHCO, AO2C, A = alkali or alk. earth metal; R4, R5, R6, R7 = H, halo, C1-6 alkyl, F3C, C1-3 alkoxy, etc.) and pharmacol. acceptable salts thereof, are prepd. To 5-(trifluoromethyl)isatin in NaOH at 90-95.degree. was added to warm soln. of 4-PhC6H4COCH2.HCl in H2O, EtOH and THF and refluxed 1.5 h to give I [R1 = [1,1'-bisphenyl]-4-yl; R2 = H2N; R3 = HO2C; R4 = R6 = R7 = H; R5 = F3C] (II). II at 50 mg/kg in a chronic graft vs. host reaction in mice showed 99% suppression. II and I are also effective in treating inflammation and joint deterioration assocd. with arthritic disease in warm-blooded animals.

IT **131745-25-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antiarthritic and immunosuppressant)

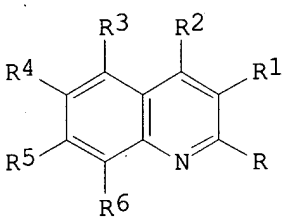
RN 131745-25-0 CA
CN 4-Quinolinecarboxylic acid, 3-amino-2-[1,1'-biphenyl]-4-yl-6-fluoro- (9CI) (CA INDEX NAME)



L20 ANSWER 52 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 113:145331 CA
TITLE: Treatment of cancer in mammals by concurrent administration of 4-quinoline carboxylic acid derivatives and interleukin-2
INVENTOR(S): Loveless, Scott Edward
PATENT ASSIGNEE(S): du Pont de Nemours, E. I., and Co., USA
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 362578	A1	19900411	EP 1989-116857	19890912
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE				
JP 02121923	A2	19900509	JP 1989-237385	19890914

PRIORITY APPLN. INFO.: US 1988-244171 19880914
OTHER SOURCE(S): MARPAT 113:145331
GI



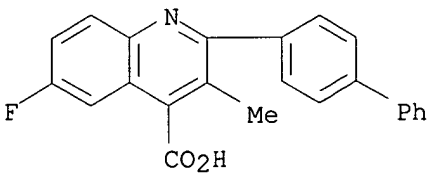
I

AB Interleukin-2 (IL-2) in combination with 4-quinolinecarboxylic acids (I, R = substituted Ph or thienylphenyl; R1 = H, alkyl, alkoxy; R2 = CO2H or carboxylate; R3, R4, R5, and R6 = H, halo, Me, CF3, SMe, Et) are useful for the treatment of solid tumors in mammals. The tumor-**inhibiting** effect of the combination of IL-2 and I exceeds the effect of either agent alone. Thus, I (R = C6H4-4-C6H4F-2; R1 = Me; R2 = CO2H; R3, R5, and R6 = H; R4 =F) (II) was prepd. from the reaction of 5-fluoroisatin with 4-(2-fluorophenyl)propiophenone in EtOH. The recombinant IL-2, differing from mature human-cell-expressed IL-2 by the presence of an N-terminal methionine residue in .apprx.50% of rIL-2 mols., was prepd. by expression of the plasmid vector pTrpE-IL2 in Escherichia coli. In mice bearing B16 melanomas, intradermal administration of 5 mg II/kg daily for 9 days commencing 12 days after tumor implantation combined with administration of rIL-2 (0.1 mg/kg/day, on days 1-5 and then twice daily on days 8-12, commencing 12 days after tumor implantation) increased survival rates more than did the administration of either agent alone. I.p. administration of the agents in animals bearing i.p. melanoma transplants was also effective. Formulations are described for administration of I as capsules, tablets, injections, or suspensions.

IT **96187-27-8**
RL: BIOL (Biological study)
(as neoplasm **inhibitor** combined with interleukin 2, metastatic melanoma in relation to)

RN 96187-27-8 CA
CN 4-Quinolinecarboxylic acid, 2-[1,1'-biphenyl]-4-yl-6-fluoro-3-methyl-

(9CI) (CA INDEX NAME)

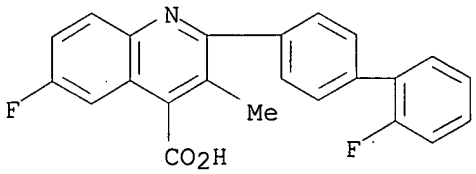


L20 ANSWER 53 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 113:182 CA
TITLE: Effects of plasma protein binding displacement on the pharmacokinetics, tissue and tumor concentrations and efficacy of brequinar, a highly protein-bound antitumor agent
AUTHOR(S): Aungst, Bruce J.; Blake, Judy A.; Rogers, Nancy J.; Dusak, Betsy A.
CORPORATE SOURCE: Du Pont Med. Prod., Wilmington, DE, 19880-0400, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1990), 253(1), 230-6
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Brequinar is a developmental antitumor agent which is highly bound to plasma proteins. The effects of plasma protein binding displacement on brequinar pharmacokinetics, tissue distribution, tumor distribution and antitumor efficacy were evaluated. Na salicylate and ibuprofen increased the percentage of free brequinar in rat serum in vitro, in proportion to their added concns. Salicylate also altered the pharmacokinetics of i.v. brequinar in rats when administered i.v. or orally at 10- or 50-fold higher doses than brequinar. At the highest salicylate/brequinar dose ratio, increases were obsd. for terminal half-life, mean residence times in the body and tissues, systemic clearance, distribution clearance, the vol. of the central compartment and vol. of distribution at steady state. Neither salicylate nor ibuprofen increased brequinar concns. in lung and muscle specimens from rats, 4 or 24 h after administration. Tumor, lung and muscle brequinar concns. in mice were also unaffected by coadministered Na salicylate, 4 or 24 h after a single i.v. brequinar dose. In rats infused for 48 h with brequinar or brequinar plus salicylate, salicylate increased the percentage of free brequinar in plasma and lungs, but total brequinar concns. were reduced. Antitumor efficacy was evaluated by measuring the survival times of mice implanted with L1210 leukemia cells. Salicylate-treated mice had a similar brequinar dose/response profile as mice not coadministered salicylate. Ibuprofen also did not increase brequinar's antitumor potency.

IT **96187-53-0**, Brequinar
RL: BIOL (Biological study)
(pharmacokinetics of and neoplasm **inhibition** by, plasma protein binding displacement effect on)

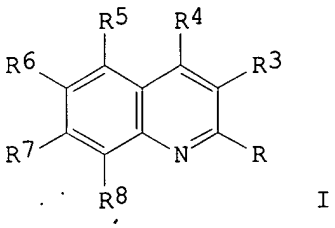
RN 96187-53-0 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 54 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 112:70040 CA
TITLE: Preparation of 4-quinolinecarboxylic acid derivatives useful for treating skin and mucoepithelial diseases
INVENTOR(S): Ackerman, Neil R.; Harris, Richard R.; Loveless, Scott E.; Neubauer, Russel H.
PATENT ASSIGNEE(S): du Pont de Nemours, E. I., and Co., USA
SOURCE: U.S., 8 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4861783	A	19890829	US 1988-186242	19880426
EP 339484	A1	19891102	EP 1989-107098	19890420
EP 339484	B1	19930120		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 84716	E	19930215	AT 1989-107098	19890420
ES 2053856	T3	19940801	ES 1989-107098	19890420
AU 8933318	A1	19891102	AU 1989-33318	19890424
AU 610469	B2	19910516		
IL 90056	A1	19930404	IL 1989-90056	19890424
DK 8901997	A	19891027	DK 1989-1997	19890425
JP 02072163	A2	19900312	JP 1989-103585	19890425
JP 2650756	B2	19970903		
KR 124817	B1	19971125	KR 1989-5406	19890425
ZA 8903086	A	19901228	ZA 1989-3086	19890426

PRIORITY APPLN. INFO.: US 1988-186242 A 19880426
EP 1989-107098 A 19890420
OTHER SOURCE(S): CASREACT 112:70040; MARPAT 112:70040
GI



I

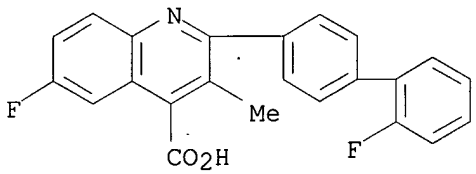
AB Skin and mucoepithelial diseases in mammals (e.g. psoriasis, lichen planus, chronic eczema, ichthyosis, pityriasis, chronic urticaria) are treated by application of the title compds. (I; R = substituted Ph or

thienyl; R3 = H, alkoxy, Me, Et; R4 = CO2H, aminoalkoxycarbonyl; R5-R8 = H, F, Cl, Br, I, Me, CF3, SMe, Et) or their salts. Thus, reaction of 4-chloroisatin with 4-phenylpropiophenone, refluxing in THF-HCl, and addn. of NaOH yielded Na 2-(1,1'-biphenyl-4-yl)-5-chloro-3-methylquinoline-4-carboxylate (II). II at 10.0 mg/kg orally **inhibited** the hyperproliferation induced by topical application of TPA to the ears of mice. Hard gelatin capsules were prepd. contg. I 50, lactose 175, talc 24, and Mg stearate 6 mg.

IT **96187-53-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for skin and mucoepithelial disease treatment)

RN 96187-53-0 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 55 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 111:186911 CA

TITLE: Anticancer quinones and quinolines: mode of action via electron transfer and oxidative stress

AUTHOR(S): Kovacic, Peter; Ames, James R.; Grogan, James W.; Hazra, Banasri; Ryan, Michael D.

CORPORATE SOURCE: Dep. Chem., Univ. Wisconsin, Milwaukee, WI, 53211, USA

SOURCE: Redox Chem. Interfacial Behav. Biol. Mol., [Proc. Int. Symp. Redox Mech. Interfacial Prop. Mol. Biol. Importance], 3rd (1988), Meeting Date 1987, 295-307. Editor(s): Dryhurst, Glenn; Niki, Katsumi. Plenum: New York, N. Y.
CODEN: 56PMAE

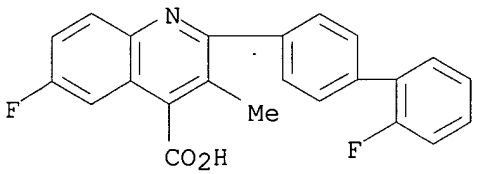
DOCUMENT TYPE: Conference

LANGUAGE: English

AB Further insights into the electron transfer (ET) mechanism of action proposed for various types of antitumor agents was gained by examg. the redox characteristics of several quinones (substituted 1,4-naphthoquinones) and quinolinium (iminium) ions from Dup 785 and camptothecin. Redn. potentials ranged from 0.0 to -0.73 V. Electrochem. data were related to structure and physiol. activity. In the quinone category the influence of hydrogen bonding and ability to lose halide are discussed. Both Dup 785 and camptothecin exhibited appreciable increases in redn. potentials at higher acidities. The values for the iminium species were of the same magnitude as for known ET agents. Model compds. showed that certain substituents in the quinoline ring favor redn. Many substances similar to Dup 785 possess biol. activity. ET and oxy radical generation have been assocd. with the action of camptothecin. The results for the quinones and the quinoline drugs are in accord with a theor. approach involving ET.

IT **96201-88-6**, Dup 785
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm **inhibition** by, electron transfer and oxidative stress in, structure in relation to)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)

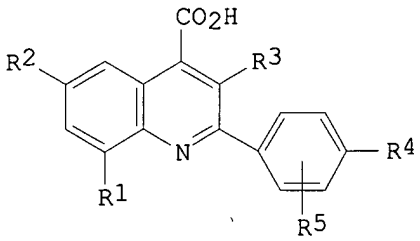


● Na

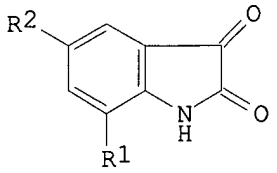
L20 ANSWER 56 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 111:97106 CA
TITLE: Substituted 2-phenyl-4-quinolinecarboxylic acids useful as antiarthritics and immunosuppressants, and a process for their preparation
INVENTOR(S): Sutherland, Leslie H.; Sloboda, Adolph E.; Child, Ralph Grassing; Poletto, John F.; Powell, Dennis W.
PATENT ASSIGNEE(S): American Cyanamid Co., USA
SOURCE: Eur. Pat. Appl., 26 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 305952	A1	19890308	EP 1988-114061	19880829
EP 305952	B1	19930602		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, NL, SE				
US 4847381	A	19890711	US 1987-90996	19870831
IL 87457	A1	19940826	IL 1988-87457	19880815
AT 90079	E	19930615	AT 1988-114061	19880829
ES 2058191	T3	19941101	ES 1988-114061	19880829
CA 1333606	A1	19941220	CA 1988-575951	19880829
DK 8804826	A	19890301	DK 1988-4826	19880830
DK 169473	B1	19941107		
FI 8803997	A	19890301	FI 1988-3997	19880830
FI 92692	B	19940915		
FI 92692	C	19941227		
NO 8803865	A	19890301	NO 1988-3865	19880830
NO 174961	B	19940502		
NO 174961	C	19940810		
AU 8821678	A1	19890302	AU 1988-21678	19880830
AU 613661	B2	19910808		
ZA 8806443	A	19890426	ZA 1988-6443	19880830
JP 01110673	A2	19890427	JP 1988-213853	19880830
JP 2760379	B2	19980528		
HU 48597	A2	19890628	HU 1988-4489	19880830
HU 202498	B	19910328		
KR 9705909	B1	19970422	KR 1988-11111	19880830
DD 282225	A5	19900905	DD 1988-319347	19880831
CS 274434	B2	19910411	CS 1988-5875	19880831

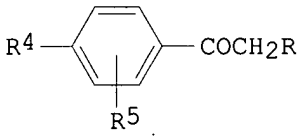
PL 156232 B1 19920228 PL 1988-274471 19880831
PRIORITY APPLN. INFO.: US 1987-90996 A 19870831
EP 1988-114061 A 19880829
OTHER SOURCE(S): CASREACT 111:97106; MARPAT 111:97106
GI



I



II

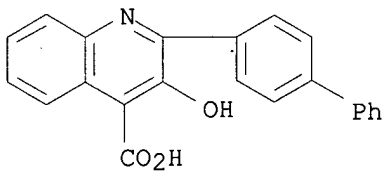


III

AB Title acids I [R1 = OH, halo, C1-3 alkyl; R2 = H, halo, CF3, C1-3 alkyl; R3 = OH, C2-6 alkanoyloxy; R4 = CF3, halo, OH, C1-6 alkyl, Ph, PhCH2, PhO, PhS, C3-6 cycloalkyl, 2,4-Cl2C6H3O, or Ph mono- or disubstituted by halo or C1-3 alkoxy; R5 = H, halo; R2 .noteq. F when R1 = H; R4 .noteq. Cl, Br, iodo, Me, or Ph when R3 = OH], useful as antiarthritics and immunosuppressive agents, are prepd. by cyclocondensation of 2,3-indolinediones II with acetophenones III. A soln. of 16.1 g II (R1 = Me, R2 = H) and 25.4 g III (R = AcO, R4 = Ph, R5 = H) in aq. EtOH contg. 16.6 g NaOH was refluxed 2.5 h, concd., dild. with H2O, filtered, and acidified to give 13.6 g I (R1 = Me, R2 = R5 = H, R3 = OH, R4 = Ph) (IV). In an adjuvant arthritis test in rats, IV reduced arthritic paw diam. from 11.8 mm (arthritic controls) to 7.6 mm, X-ray erosion scores from 3.12 to 1.95, and cartilage space scores from 3.27 to 2.32.

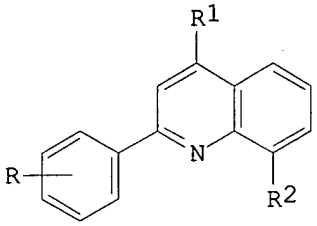
IT **122262-54-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antiarthritic and immunosuppressant)

RN 122262-54-8 CA
CN 4-Quinolinecarboxylic acid, 2-[1,1'-biphenyl]-4-yl-3-hydroxy- (9CI) (CA INDEX NAME)



L20 ANSWER 57 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 110:135063 CA
TITLE: Potential antitumor agents. 57. 2-Phenylquinoline-8-carboxamides as minimal DNA-intercalating antitumor agents with in vivo solid tumor activity
AUTHOR(S): Atwell, Graham J.; Baguley, Bruce C.; Denny, William A.

CORPORATE SOURCE: Sch. Med., Univ. Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (1989), 32(2), 396-401
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 110:135063
GI

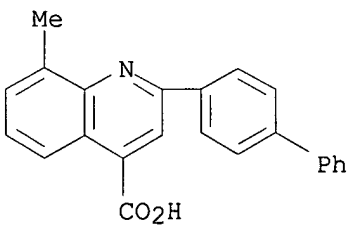


I

AB A series of phenyl-substituted derivs. of the minimal DNA-intercalating agent N-[2-(dimethylamino)ethyl]-2-phenylquinoline-8-carboxamide were synthesized and evaluated for in vivo antitumor activity, in a continuing search for active compds. of this class with the lowest possible DNA assocn. consts. Substitution on the 2'-position of the Ph ring gave compds. of lower DNA binding ability that did not intercalate DNA, indicating that it is necessary for the Ph ring to be essentially coplanar with the quinoline for intercalative binding. An extensive series of 4'-substituted derivs. was evaluated, but there was no overall relationship between biol. activity and substituent lipophilic or electronic properties. However, several compds. showed good solid tumor activity, with the 4'-aza deriv. being clearly superior to the parent compd., effecting about 50% cures in both leukemia and solid tumor models. Thus, cyclization of 7-methylisatin with RC6H4Ac gave quinoline I (R = Cl, H, p-Br, p-I, p-Ph, p-OMe, etc.; R1 = CO2H; R2 = Me) which were decarboxylated with Cu and oxidized to give I (R1 = H, R2 = CO2H), which were amidated with Me2NCH2CH2NH2 to give I [R2 = CONH(CH2)2NMe2].

IT **107027-46-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and decarboxylation of)

RN 107027-46-3 CA
CN 4-Quinolinecarboxylic acid, 2-[1,1'-biphenyl]-4-yl-8-methyl- (9CI) (CA INDEX NAME)



L20 ANSWER 58 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 109:156286 CA

TITLE: Freeze-dried pharmaceutical compositions of phenylquinoline carboxylic acids
INVENTOR(S): Wu, Chien Chin
PATENT ASSIGNEE(S): du Pont de Nemours, E. I., and Co., USA
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

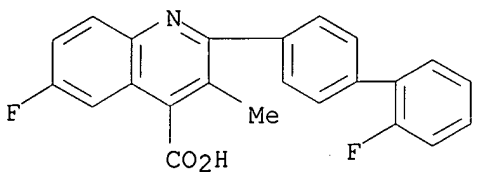
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 261426	A1	19880330	EP 1987-112367	19870826
EP 261426	B1	19921104		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 4889862	A	19891226	US 1987-60203	19870610
CA 1312824	A1	19930119	CA 1987-544796	19870818
FI 8703701	A	19880229	FI 1987-3701	19870826
FI 90824	B	19931231		
AT 81967	E	19921115	AT 1987-112367	19870826
ES 2052530	T3	19940716	ES 1987-112367	19870826
DK 8704478	A	19880229	DK 1987-4478	19870827
DK 168655	B1	19940516		
NO 8703626	A	19880229	NO 1987-3626	19870827
AU 8777622	A1	19880303	AU 1987-77622	19870827
AU 602715	B2	19901025		
JP 63115816	A2	19880520	JP 1987-211503	19870827
HU 45398	A2	19880728	HU 1987-3780	19870827
HU 199289	B	19900228		
IL 83662	A1	19910916	IL 1987-83662	19870827
SU 1837878	A3	19930830	SU 1987-4203218	19870827
ZA 8706446	A	19890426	ZA 1987-6446	19870828
LV 10686	B	19951020	LV 1993-322	19930512

PRIORITY APPLN. INFO.: US 1986-901254 19860828
US 1987-60203 19870610
EP 1987-112367 19870826

AB A freeze-dried pharmaceutical compn. of antitumor phenylquinolinecarboxylic acids comprises bile salts as a solubilizer to prevent compds. from pptg. during the prepn. of bulk soln. and upon reconstituting from the freeze-dried form. A freeze-dried powder contained 6-fluoro-2-(2'-fluoro-1'-biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid Na salt 100, Na cholate 40, and glycine 40 mg. The powder was sealed in vials and remained stable during storage for 6 mo at 25.degree.. The powder was reconstituted with 4 mL water for injection and the soln. appeared clear for 24 h with little change in drug concn. The antitumor activity of the compd. against L1210 leukemia in mice was not affected by Na cholate and glycine.

IT **96201-88-6**
RL: BIOL (Biological study)
(antitumor freeze-dried powder compn. of, stabilizers in, bile salts as)

RN 96201-88-6 CA
CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 59 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 109:54674 CA
TITLE: Preparation of 2-phenyl-4-quinolinecarboxylates as antitumor agents
INVENTOR(S): Hesson, David P.
PATENT ASSIGNEE(S): du Pont de Nemours, E. I., and Co., USA
SOURCE: U.S., 19 pp. Cont.-in-part of U.S. Ser. No. 605,104, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4680299	A	19870714	US 1985-727808	19850426
AU 8430852	A1	19850124	AU 1984-30852	19840719
AU 583793	B2	19890511		
ZA 8405594	A	19860326	ZA 1984-5594	19840719
CA 1288436	A1	19910903	CA 1984-459263	19840719
DK 8403587	A	19850123	DK 1984-3587	19840720
FI 8402928	A	19850123	FI 1984-2928	19840720
FI 86987	B	19920731		
FI 86987	C	19921110		
NO 8402969	A	19850123	NO 1984-2969	19840720
NO 167510	B	19910805		
NO 167510	C	19911113		
JP 60042367	A2	19850306	JP 1984-149802	19840720
JP 05019549	B4	19930317		
HU 35248	A2	19850628	HU 1984-2824	19840720
HU 194832	B	19880328		
ES 534509	A1	19850901	ES 1984-534509	19840720
SU 1393314	A3	19880430	SU 1984-3776940	19840720
IL 72471	A1	19881115	IL 1984-72471	19840720
SU 1452480	A3	19890115	SU 1986-4000869	19860106
US 5032597	A	19910716	US 1987-30421	19870326

PRIORITY APPLN. INFO.:
US 1983-516319 19830722
US 1984-605104 19840430
US 1985-727808 19850426

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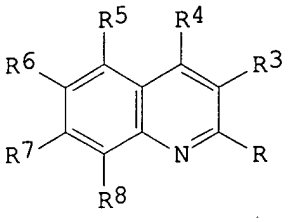


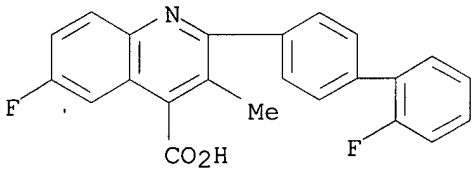
I

AB Title compds. I [R = (un)substituted cyclohexylphenyl, -phenoxyphenyl, -benzylphenyl, phenylthienyl, etc; R3 = H, C1-3 alkoxy; C1-2 alkyl; R4 = HO2C, its aminoalkyl ester; R5, R6, R7, R8 = H, Br, Cl, F, iodo, Me, F3C, MeS, Et; .gtoreq. 2 of R5, R6, R7, R8 = H] and their salts, were prepd. Pfitzinger reaction of 5-fluoroisatin with 4-cyclohexylpropiophenone gave I (R = 4-cyclohexylphenyl; R3 = Me; R4, R5, R7, R8 = H; R6 = F) (II). II, at 25 mg/kg i.p., increased survival time of mice implanted with melanotic melanoma B16 25-27% over controls.

IT **96202-41-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(Pfitzinger reaction of)

RN 96202-41-4 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, potassium salt (9CI) (CA INDEX NAME)



● K

L20 ANSWER 60 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 109:16469 CA

TITLE: Application of a new preclinical drug screening system for cancer of the large bowel

AUTHOR(S): Scheithauer, Werner; Moyer, Mary P.; Clark, Gary M.; Von Hoff, Daniel D.

CORPORATE SOURCE: Sch. Med., Vienna Univ., Vienna, Austria

SOURCE: Cancer Chemotherapy and Pharmacology (1988), 21(1), 31-4
CODEN: CCPHDZ; ISSN: 0344-5704

DOCUMENT TYPE: Journal

LANGUAGE: English

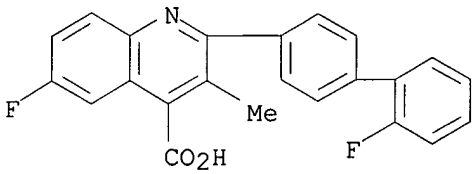
AB A prospective evaluation of 3 human continuous colorectal cancer cell lines and a new semiautomated radiometric technique (Bactec system) as a primary screening procedure for cytotoxic compds. with activity against large bowel cancer is reported. COLO 320DM, Ht-29, and the metastatic OM-1 colon cancer cell lines, that have yielded clin. relevant information on drug sensitivity patterns in humans, were tested against 11 new compds. currently tested in clin. trials. The results suggest that trimetrexate, DUP-785, didemnin B, and flavone-8-acetic acid may be clin. effective for

the treatment of colorectal cancer.

IT **96201-88-6**, DUP-785
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(colorectal cancer sensitivity to, testing of)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)

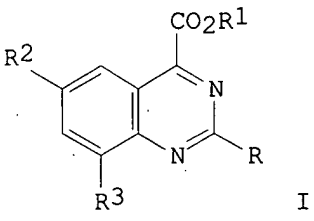


● Na

L20 ANSWER 61 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 106:156491 CA
TITLE: Preparation of phenylquinazolinecarboxylic acids, their antitumor activity, and pharmaceutical compositions containing them
INVENTOR(S): Hesson, David P.
PATENT ASSIGNEE(S): du Pont de Nemours, E. I., and Co., USA
SOURCE: U.S., 10 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4639454	A	19870127	US 1985-692412	19850117

PRIORITY APPLN. INFO.: US 1985-692412 19850117
OTHER SOURCE(S): CASREACT 106:156491
GI



I

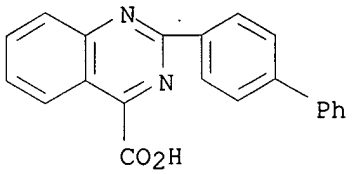
AB 2-Phenyl-4-quinazolinecarboxylic acids I [R = substd. Ph; R1 = H, (CH2)nNR42 (R4 = H, C1-3 alkyl); R2, R3 = H, halogen, CF3, C1-2 alkyl; n = 2-4], useful as antitumor agents, are prepd. K isatinate, prepd. from isatin, was acylated with 4-biphenylcarbonyl chloride to give 2-(1,1'-biphenyl-4-ylcarbonylamino)-.alpha.-oxobenzeneacetic acid, which

was cyclized with NH3 to give I (R = 1,1'-biphenyl-4-yl, R1-R3 = H)(II). II at 200 mg/kg increased survival time of mice injected with 105 L1210 leukemia cells by 165%. A parenteral compn. suitable for injection contains 1.5% by wt. of I in 10% by vol. propylene glycol and water. The soln. is made isotonic with NaCl and sterilized.

IT **107512-70-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and acidification of)

RN 107512-70-9 CA

CN 4-Quinazolinecarboxylic acid, 2-[1,1'-biphenyl]-4-yl-, ammonium salt (9CI) (CA INDEX NAME)



L20 ANSWER 62 OF 63 CA COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 104:28500 CA

TITLE: Activity of a novel 4-quinolinecarboxylic acid, NSC 368390 [6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinolinecarboxylic acid sodium salt], against experimental tumors

AUTHOR(S): Dexter, Daniel L.; Hesson, David P.; Ardecky, Robert J.; Rao, Ganti V.; Tippett, Davette L.; Dusak, Betsy A.; Paull, Kenneth D.; Plowman, Jacqueline; Delarco, Barbara M.; et al.

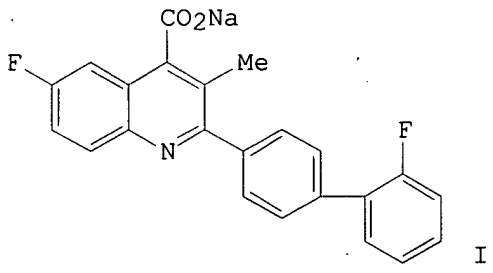
CORPORATE SOURCE: Biomed. Prod. Dep., E. I. du Pont de Nemours and Co., Inc., Wilmington, DE, 19898, USA

SOURCE: Cancer Research (1985), 45(11, Pt. 1), 5563-8
CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

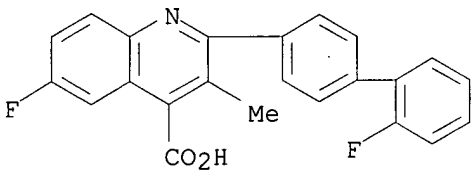
AB In mice bearing L1210 leukemia, DuP-785 (NSC 368390)(I) [**96201-88-6**] caused an increase in life span of >80%; the activity

was schedule dependent, and the compd. was equally efficacious when administered i.p., i.v., s.c., or orally. In tests against human tumors xenografted under the renal capsule of nude mice, I when injected i.p. in doses of 20-40 mg/kg daily for 9 days **inhibited** the growth of the MX-1 breast, LX-1 lung, BL/STX-1 stomach, and CX-1 colon carcinomas by >90%. I also **inhibited** the growth of 3 distinct human colon carcinomas, the HCT-15, clone A, and DLD-2 tumors, growing s.c. in nude mice. An i.p. dose of 25 mg/kg given daily for 9 days **inhibited** the growth of the DLD-2 colon cancer by 98%. 1-.beta.-D-Arabinofuranosylcytosine and adriamycin were ineffective, and fluorouracil was only moderately effective against these colon tumors. Because of its good activity against human colon tumors and other human carcinomas and its water soly., I is being developed as a Phase 1 anticancer agent.

IT **96201-88-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm-**inhibiting** activity of, of humans and lab. animals)

RN 96201-88-6 CA

CN 4-Quinolinecarboxylic acid, 6-fluoro-2-(2'-fluoro[1,1'-biphenyl]-4-yl)-3-methyl-, sodium salt (9CI) (CA INDEX NAME)



● Na

L20 ANSWER 63 OF 63 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 102:191177 CA
TITLE: Phenylquinolinecarboxylic acids and derivatives as antitumor agents
INVENTOR(S): Hesson, David Paul
PATENT ASSIGNEE(S): du Pont de Nemours, E. I., and Co. , USA
SOURCE: Eur. Pat. Appl., 67 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 133244	A2	19850220	EP 1984-108523	19840719
EP 133244	A3	19851211		
EP 133244	B1	19901205		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
AU 8430852	A1	19850124	AU 1984-30852	19840719
AU 583793	B2	19890511		
ZA 8405594	A	19860326	ZA 1984-5594	19840719
AT 58834	E	19901215	AT 1984-108523	19840719
CA 1288436	A1	19910903	CA 1984-459263	19840719
DK 8403587	A	19850123	DK 1984-3587	19840720

FI 8402928	A	19850123	FI 1984-2928	19840720
FI 86987	B	19920731		
FI 86987	C	19921110		
NO 8402969	A	19850123	NO 1984-2969	19840720
NO 167510	B	19910805		
NO 167510	C	19911113		
JP 60042367	A2	19850306	JP 1984-149802	19840720
JP 05019549	B4	19930317		
HU 35248	A2	19850628	HU 1984-2824	19840720
HU 194832	B	19880328		
ES 534509	A1	19850901	ES 1984-534509	19840720
SU 1393314	A3	19880430	SU 1984-3776940	19840720
IL 72471	A1	19881115	IL 1984-72471	19840720
SU 1452480	A3	19890115	SU 1986-4000869	19860106

PRIORITY APPLN. INFO.:

US 1983-516319 19830722
US 1984-605104 19840430
EP 1984-108523 19840719

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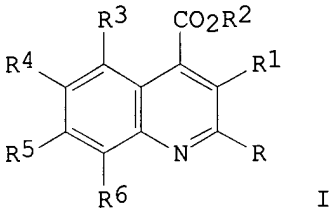


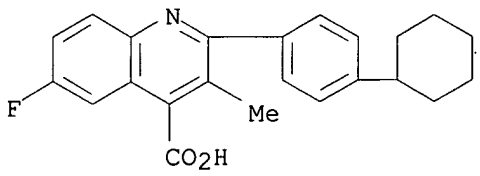
I

AB Antitumor pharmaceuticals comprise the title compds. I (R = substituted heterocycle or substituted Ph; R1 = H, C1-3 alkoxy, C1-3 alkylthio; C1-3 (un)substituted alkyl; R2 = H, metal salt or amine group; R3, R4, R5, and R6 = H, halo, Me, CF3, etc.) and are prepd. in general by condensation of an appropriate isatin with a ketone (Pfitzinger reaction). Thus, 2-(4-cyclohexylphenyl)-6-fluoro-3-methylquinoline-4-carboxylic acid (I; R = 4-cyclohexylphenyl, R1 = Me, R2, R3, R4, and R5 = H, R6 = F) [**96187-26-7**], prepd. by condensation of 5-fluoroisatin [443-69-6] with 4-cyclohexylpropiophenone [59721-67-4] in the presence of KOH, **inhibited** the growth of human colon carcinoma cells in vitro. Examples of capsule, injectable, suspension, and tablet formulations are given.

IT **96187-26-7P**
RL: THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as antitumor agent, for pharmaceuticals)

RN 96187-26-7 CA

CN 4-Quinolinecarboxylic acid, 2-(4-cyclohexylphenyl)-6-fluoro-3-methyl- (9CI) (CA INDEX NAME)



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L3         1073 S L1 FULL

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L4          202 S L3
L5          581 S FLAVIVIRIDAE OR RHABDOVIRIDAE OR PARAMYXOVIRIDAE
L6            1 S L4 AND L5
L7          201 S L4 NOT L6
L8       451560 S VIRUS OR INFECT?
L9           13 S L7 AND L8
L10         188 S L7 NOT L9
L11     3299945 S DRUG? OR TREAT?
L12         125 S L10 AND L11
L13         553 S DIHYDROOROTATE?
L14          38 S L13 AND L10
L15         150 S L10 NOT L14
L16      146870 S DEHYDROGENASE?
L17           8 S L15 AND L16
L18         142 S L15 NOT L17
L19     1562762 S INHIBIT?
L20          63 S L18 AND L19

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